Northera™ (Droxidopa) Advisory Committee Briefing Document

NDA 203202

Cardiovascular and Renal Drugs Advisory Committee Meeting

14 January 2014

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ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

EXECUTIVE SUMMARY

This document summarizes data in support of Northera (droxidopa) Capsules for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in patients with primary autonomic failure (Parkinson's disease [PD], Multiple System Atrophy [MSA] and Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (DβH) Deficiency, and Non-Diabetic Autonomic Neuropathy (NDAN).

INTRODUCTION

nOH, defined by a reduction in standing systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing (Consensus Statement, 1996), is caused by a variety of neurodegenerative conditions (PD, MSA, PAF), NDAN, and congenital neurological disorders, occurs in approximately 80,000 patients in the United States (US [Colosimo et al, 1995]) and is, therefore, considered an Orphan Disease population. Despite the heterogeneity in the overall nOH patient population, the disorders associated with this condition all share a common pathophysiology, which is an inadequate norepinephrine (NE) response from sympathetic vasomotor neurons, resulting in autonomic failure and generalized blood pressure (BP) dysregulation (Freeman et al, 2011). As a result, these patients often experience both hypotension upon standing as well as hypertension when lying down.

UNMET MEDICAL NEED

Symptomatic nOH is a severely debilitating condition that can substantially reduce a patient's quality of life, and is associated with an increased risk of mortality, stroke, and myocardial ischemia. Dizziness, which characteristically presents as lightheadedness, or presyncope, is the cardinal symptom of nOH and results from cerebral hypoperfusion upon standing (Mathias et al, 1999) due to an inadequate release or utilization of NE from the sympathetic vasomotor neurons, leading to limited vasoconstriction and a decrease in BP upon assuming an upright posture. Patients may also experience syncope or lose consciousness and fall, greatly increasing the risk of significant physical injury including hip fracture and head trauma (Goldstein and Sharabi, 2009), factors that contribute to morbidity, disability, or death (Lahrmann et al, 2006). Fear of falling can result in patients limiting their activities, which leads to a host of complications ranging from a reduction in muscle mass and overall fitness to depression, feelings of social isolation, and loss of independence (Vellas et al, 1997; Sclatter and Alagiakrishnan, 2004). Taken together, the symptomatic consequences of nOH can substantially reduce patients' quality of life (Mathias, 2008; Maule et al, 2007; Magerkurth et al, 2005).

In addition to the complications associated with cerebral hypoperfusion upon standing, patients with nOH are at risk of developing supine hypertension. It has been demonstrated that more than 50% of patients with autonomic failure experience hypertension when supine (Shannon et al, 1997; Shibao et al, 2006). Supine hypertension causes hypertensive heart disease (Maule et al, 2006), brain ischemia and hemorrhage (Sandroni et al, 2001), papilloedema, and hypertensive retinopathy (Maule et al, 2007). Left ventricular hypertrophy has been associated with supine hypertension in patients with primary autonomic failure (Vagaonescu et al, 2000). Elevated nighttime SBP is independently and significantly associated with cardiovascular mortality

(Pathak et al, 2004). Furthermore, nighttime pressure natriuresis and the resulting volume depletion can exacerbate symptoms associated with nOH (Jordan et al, 1999).

As a result of the range of problems that are attributed to autonomic failure, the prognosis and overall clinical outcome of patients with nOH is poor. In a 1-year observation study of 31 patients with autonomic failure and 26 age-matched PD patients without autonomic failure, 5 of the 31 patients (16.1%) with autonomic failure died during the 1-year observation period compared with none of the age-matched PD patients without autonomic failure (Pathak et al, 2005). Other longitudinal studies have also shown that chronic orthostatic hypotension (OH) increases the risk of mortality (Raiha et al, 1995; Davis et al, 1987; Masaki et al, 1998).

Current Therapies

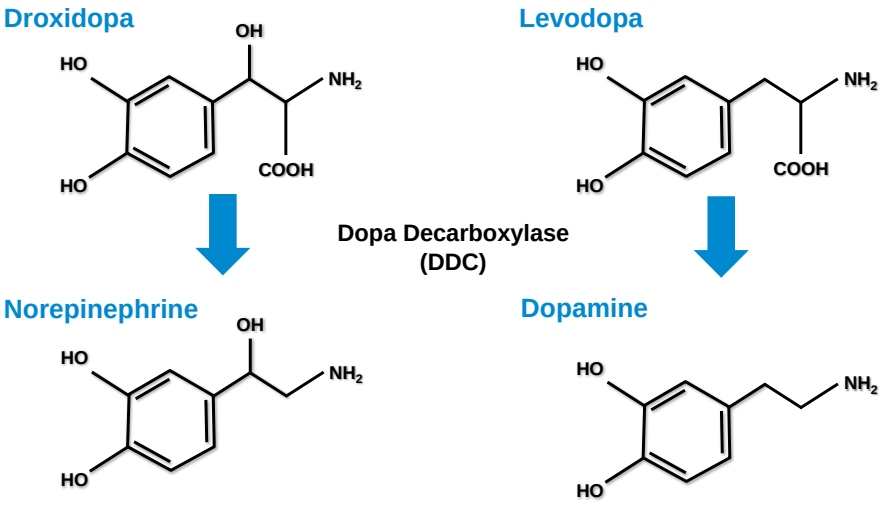
Only 1 drug, midodrine, has been approved by the Food and Drug Administration (FDA) for the treatment of symptomatic OH; however, its approval was based on BP as a surrogate outcome measure for symptomatic improvement. While BP is important in the pathophysiology of nOH, it is not validated as a surrogate endpoint for therapeutic (i.e., clinical) benefit and is no longer considered an acceptable primary endpoint by the Division of Cardiovascular and Renal Products (DCRP). To date, no studies have been conducted which demonstrate midodrine improves the symptoms of nOH. The use of midodrine has significant limitations, including its association with an increased incidence of supine hypertension and other adverse events (AEs). Furthermore, midodrine is not effective in all patients, thereby requiring physicians to often prescribe non-approved medications such as fludrocortisone, a medication which itself is also associated with inconsistent effectiveness along with potentially serious side effects (supine hypertension, congestive heart failure, cardiotoxicity, and hypokalemia).

In conclusion, there is a significant unmet need for pharmacotherapies proven to provide clinical benefit (i.e., a reduction in symptoms and their impact on the ability of patients to perform activities of daily living) and that have a favorable side effect profile, particularly with respect to the exacerbation of supine hypertension.

DROXIDOPA MECHANISM OF ACTION, PROPOSED INDICATION, AND DOSING INSTRUCTIONS

Droxidopa is an orally administered, synthetic catecholamine acid pro-drug that is converted to NE and thereby directly addresses the root cause of nOH. Thus, it is a neurotransmitter replacement therapy analogous to levodopa which is converted to the neurotransmitter dopamine in the treatment of movement disorders (Figure 1-1).

Figure 1-1 Droxidopa: Prodrug of Norepinephrine



Chelsea is proposing the following indication for NORTHERA™ (droxidopa) Capsules:

> NORTHERA™ is indicated for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in adult patients with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)], Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN). The clinical benefits of NORTHERA are improvements in dizziness, lightheadedness, feeling faint, or "feeling like you might black out." Clinical benefit has been demonstrated in short-term trials; long-term benefits have not been verified.

Chelsea is proposing the following dosage and administration for the package insert for NORTHERA™ (droxidopa) Capsules:

> The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily (TID): upon arising in the morning; midday; and late afternoon at least 3 to 4 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Patients should take NORTHERA consistently either with food or without food. Dose optimization should be based on a patient's symptomatic response and clinical condition. The dose may be increased in increments of 100 mg TID every 24 to 48 hours up to a maximum dose of 600 mg TID (i.e., a maximum total daily dose of 1800 mg).
>
> Dose optimization should be based on a patient's symptomatic response after at least one full day on therapy. During clinical trials, dose optimization was usually conducted on a daily basis and completed within a 10 day period. Supine BP should be monitored regularly and more frequently when changing dose. The dose of NORTHERA should be reduced or administration stopped if supine BP increases excessively. The last dose should be taken at least 3-4 hours before bedtime.

Patients who miss a dose of NORTHERA should take their next scheduled dose. Patients should not take more than the prescribed total daily amount of NORTHERA in any 24-hour period.

DROXIDOPA CLINICAL DEVELOPMENT PROGRAM

Chelsea licensed droxidopa from Dainippon Sumitomo Pharma (DSP) Co., Ltd., Japan, where it has been on the market for the treatment of nOH for over 20 years. The Chelsea development program included the following 10 clinical studies:

Pivotal Phase 3 Studies

- Study 301: A 1-week, double-blind, multi-center, randomized, placebo-controlled, parallel-group, induction design study to assess the effect of droxidopa on nOH symptoms and their impact on activities of daily living (N=162)

- Study 306B: An 8-week double-blind, multi-center, randomized, placebo-controlled, parallel-group, induction design study to assess the effect of droxidopa on nOH symptoms and their impact on activities of daily living in patients with PD (N=147)

As described in Section 6.1.2.1, Study 306 underwent an interim analysis of the first 51 patients; the interim analysis resulted in a separate, locked dataset from which new hypotheses were generated. Study 306B was the continuation of the initial study to test these new hypotheses.

Of note, in each of the pivotal studies, all patients entered a dose titration/optimization period (which was open-label for Study 301 [see Section 6.1.1] and double-blind for Study 306B [see Section 6.1.2]), where their doses were titrated to effect based on their individualized efficacy and safety response.

Supportive Studies

- Study 302: A 2-week, double-blind, multi-center, randomized, placebo-controlled, parallel-group, withdrawal design study to assess the effect of droxidopa on nOH symptoms and their impact on activities of daily living (N=101)

- Study 306A (also called Interim Analysis Dataset): An 8-week, double-blind, multi-center, randomized, placebo-controlled, parallel-group, induction design study to assess the effect of droxidopa on nOH symptoms and their impact on activities of daily living in patients with PD (N=51)

- Study 303: A 12-month, open-label extension study to assess the long-term safety and efficacy of droxidopa, which included a 2-week randomized-withdrawal period (N=102)

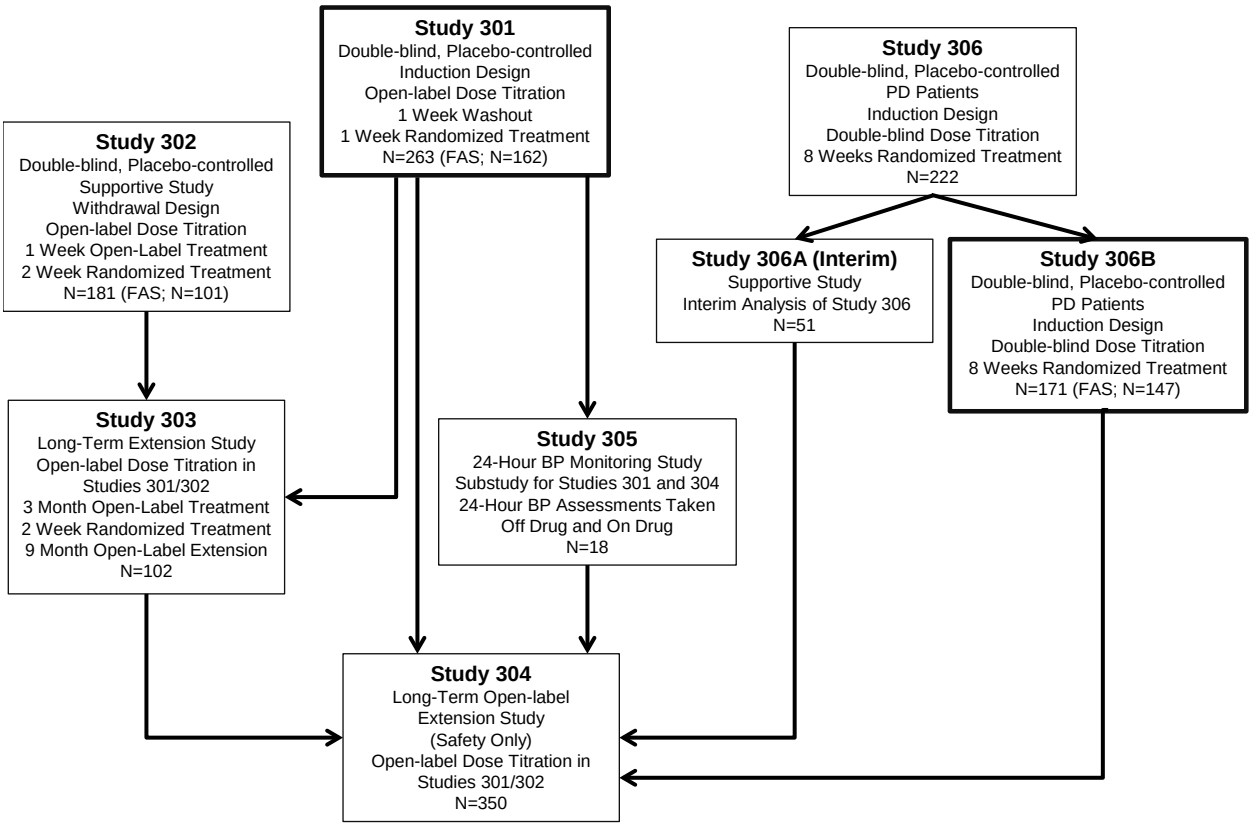
- Study 304: An open-label extension study (mean duration of exposure of approximately 1 year) to assess the long-term safety of droxidopa (N=350)

- Study 305: A 24-hour, ambulatory BP monitoring study to assess the cardiovascular safety of droxidopa in a subset of patients originally enrolled in Study 301 (N=18)

- Study 101: A Phase 1 pharmacokinetic (PK) and food effect study in healthy elderly volunteers (N=24)
- Study 102: A dedicated, thorough QTc (QT interval corrected) study (N=52)
- Study 104: A Phase 1 bioequivalence (BE) study in healthy volunteers (N=24)

Figure 1-2 provides the basic design of each Phase 3 study and illustrates the path by which patients could rollover from one study to the next.

Figure 1-2 Chelsea-Sponsored Phase 3 Droxidopa Studies



KEY REGULATORY HISTORY

Droxidopa was granted Orphan Drug designation by the Office of Orphan Products Development on 17 January 2007. The Investigational New Drug (IND) Application for droxidopa was submitted on 24 September 2007, and Fast-Track designation was granted on 07 August 2008. The original New Drug Application (NDA) was submitted in September of 2011 and the DCRP Advisory Committee met on 23 February 2012 (7 to 4 votes favoring approval, 1 abstention, 1 non-vote).

On 28 March 2012, the DCRP issued a Complete Response (CR) Letter citing inconsistencies in the overall findings and disproportionate site effects in Study 301 as the basis for requiring a second study confirming the safety and efficacy of droxidopa. After multiple discussions with

the Agency in 2012-2013, Chelsea resubmitted the NDA with an additional trial, Study 306B, to address the Agency's request for more data. A full description of regulatory events is provided in Section 5 of this Briefing Document.

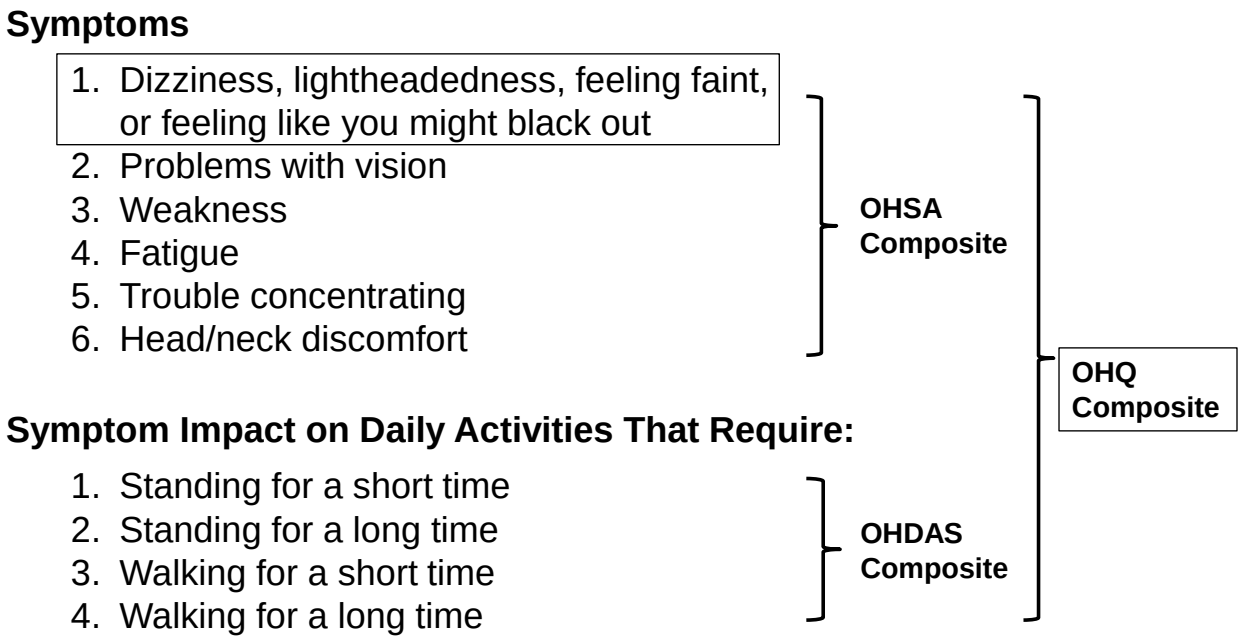
KEY EFFICACY ENDPOINTS

Prior to the start of its Phase 3 trials, Chelsea was informed by the DCRP that they could not use increases in BP as a primary endpoint for approval but, rather, needed to demonstrate symptomatic benefits. In agreement with the FDA Chelsea chose the Orthostatic Hypotension Questionnaire (OHQ) composite score, the only validated scale for nOH, as the primary endpoint for Study 301. Details regarding the OHQ are presented in Section 4.4.1 of this Briefing Document and the validation of the OHQ was published in 2012 by Kaufmann et al.

Following the original NDA submission, the FDA's Study Endpoints and Label Development (SEALD) group identified the Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 (dizziness/lightheadedness), as representing the cardinal symptom of nOH, and providing the best measurement of disease-defining symptoms of nOH. Based on this guidance, the Sponsor used OHSA Item 1 as the primary endpoint for its additional clinical study, Study 306B.

The OHQ is composed of 10 individual items as shown in Figure 1-3. Each item is scored on a Likert scale from 0 to 10, with 10 being the most severe. Comparing the calculated minimally important difference (MID) across multiple methods and studies, we conclude that a change of between 1.1 and 2.5 units in OHSA Item 1 is clinically meaningful to a patient. For additional information on clinical meaningfulness see Section 4.4.1.1.

Figure 1-3 The OHQ Scale



OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

EFFICACY RESULTS

Pivotal, Short-Term Efficacy Studies

The overall data from Studies 301 and 306B, as well as the supportive Study 302, demonstrate that droxidopa provides consistent short-term benefits for the treatment of symptomatic nOH.

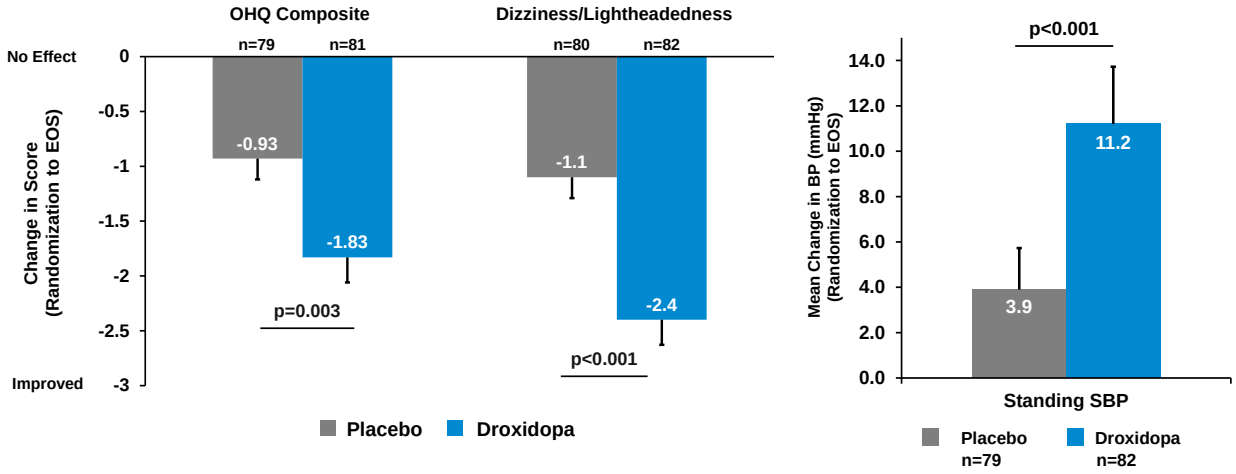
Study 301

A complete discussion of efficacy results from Study 301, including details regarding analysis sets and statistical methodology, is located in Section 6.1.1 of this Briefing Document.

In Study 301, the mean changes from Randomization to End of Study (i.e., Week 1) in the OHQ composite score (the primary endpoint) and OHSA Item 1 (a key secondary endpoint) showed statistically significant benefits favoring droxidopa (OHQ composite score: 0.90 units favoring droxidopa [p=0.003]; OHSA Item 1: 1.3 units favoring droxidopa [p<0.001]; Figure 1-4).

This study also demonstrated statistically significant improvements in standing SBP after 1 week of treatment (7.3 mmHg favoring droxidopa [p<0.001]; Figure 1-4).

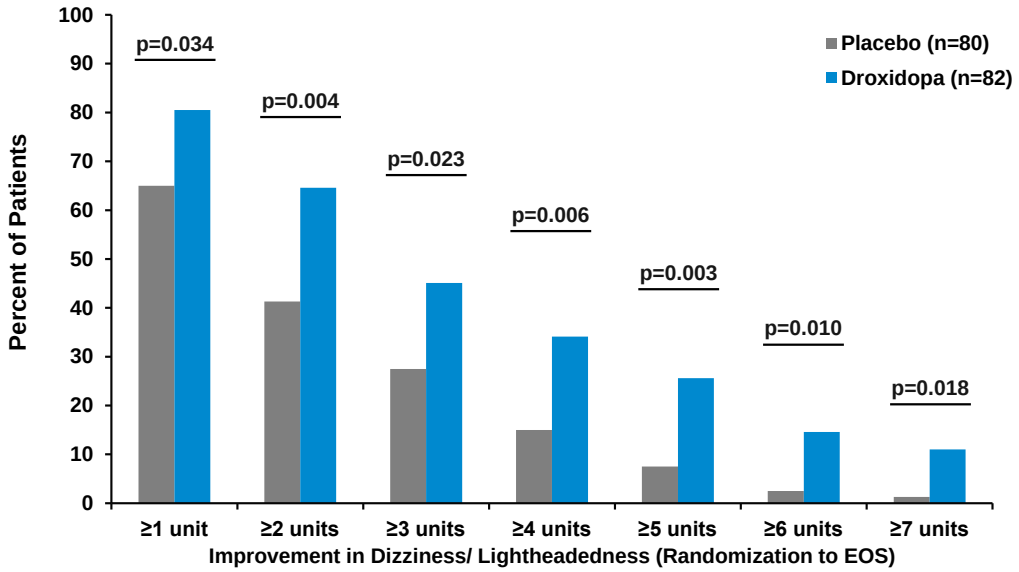
Figure 1-4 Study 301: OHQ, Dizziness (OHSA Item 1), and Standing SBP



ANCOVA=Analysis of covariance; EOS=End of Study; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SBP=Systolic blood pressure.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using a parametric ANCOVA (OHQ) or non-parametric ANCOVA (OHSA Item 1 and SBP) using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for Randomization value as a covariate.

Based on results from a *post-hoc* analysis, Study 301 demonstrated treatment differences in favor of droxidopa based on unit improvements from Randomization to End of Study in the OHSA Item 1 score regardless of the unit change of the response ($p \leq 0.034$; Figure 1-5).

Figure 1-5 Study 301: Dizziness (OHSA Item 1) Responders Analysis



EOS=End of Study; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Response assessed by Fisher's Exact test.

Limitations of Study 301

The Agency stated in its CR Letter that "the disproportionate contribution of Site 507 to the overall results of Study 301 diminishes the persuasiveness of the study." In correspondence subsequent to the CR Letter, the Agency raised additional concerns about Site 505. However, the Sponsor conducted numerous sensitivity analyses and concluded that regardless of the data from Sites 507 and 505, Study 301 conclusively demonstrates the short-term efficacy of droxidopa (refer to Section 6.1.1.5).

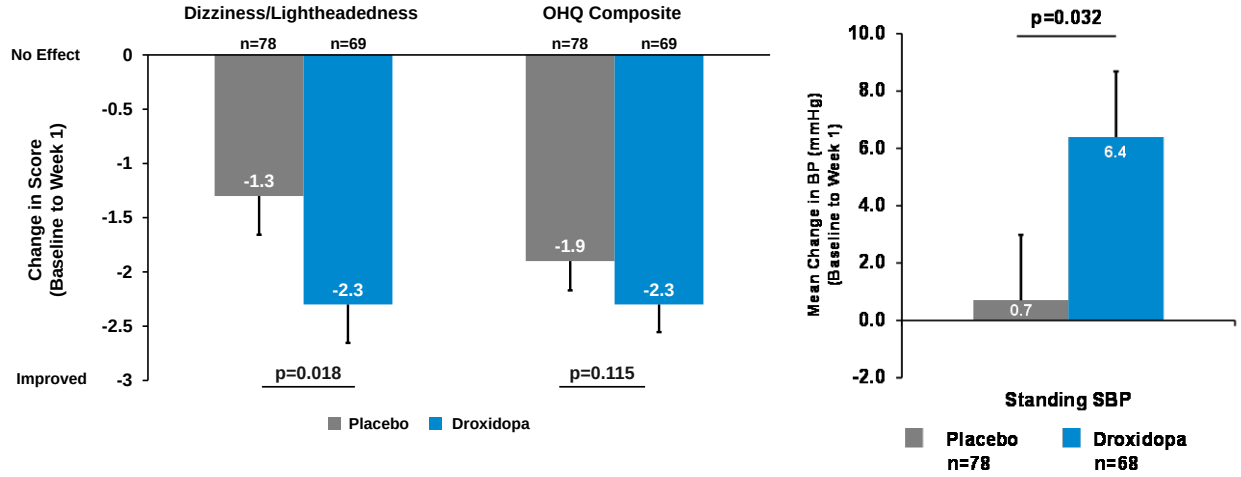
Study 306B

A complete discussion of efficacy results from Study 306B, including details regarding analysis sets and statistical methodology, is located in Section 6.1.2 of this Briefing Document.

Similar to the results from Study 301, in Study 306B the mean change from Baseline to Week 1 in OHSA Item 1 (the primary endpoint) showed statistically significant benefits favoring droxidopa (1.0 units favoring droxidopa [p=0.018]). While a treatment difference in favor of droxidopa was observed at Week 1 for the OHQ composite score (an exploratory endpoint in this study; 0.4 units), this difference was not statistically significant (p=0.115; Figure 1-6).

Similar to Study 301, a statistically significant improvement in standing SBP was observed after 1 week of treatment (5.7 mmHg favoring droxidopa [p=0.032]).

Figure 1-6 Study 306B: Dizziness (OHSA Item 1), OHQ, and Standing SBP

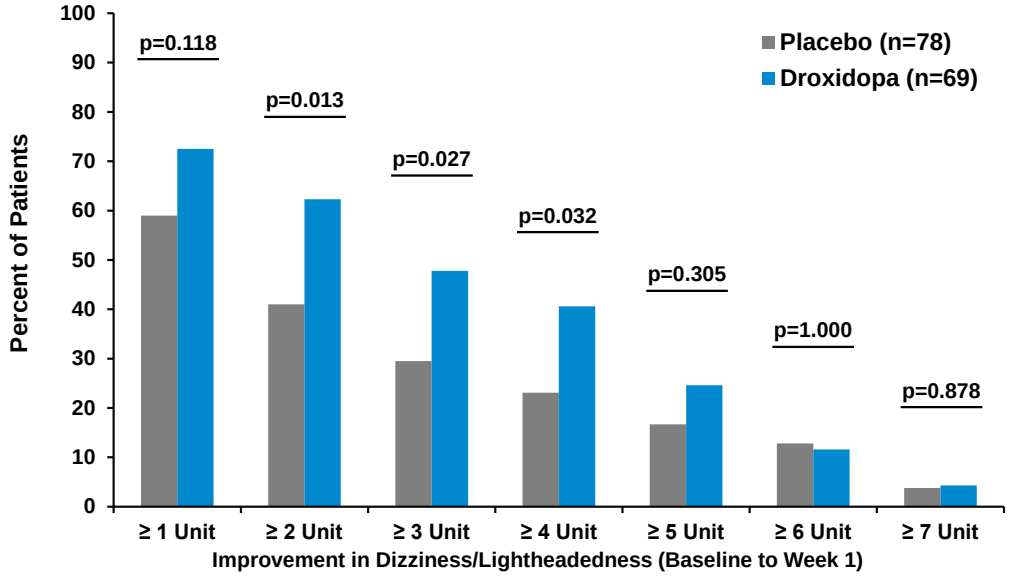


OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SBP=Systolic blood pressure.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using a parametric ANCOVA (OHQ) or non-parametric ANCOVA (OHSA Item 1 and SBP) using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for Randomization value as a covariate.

In addition, similar to results observed in Study 301, a *post-hoc* analysis of Study 306B revealed treatment differences in favor of droxidopa based on unit improvements from Randomization to End of Study in the OHSA Item 1 score for the ≥ 1-, 2-, 3-, 4-, and 5-unit improvement categories (Figure 1-7).

Figure 1-7 Study 306B: Dizziness (OHSA Item 1) Responders Analysis



OHSA=Orthostatic Hypotension Symptom Assessment.

Note: Response assessed by Fisher's Exact test.

Falls and Falls Related Injuries

Data on falls were prospectively collected via electronic patient diaries in Study 306B. Study 306B demonstrated that patients in the droxidopa group compared with the placebo group had a lower rate of falls (0.4 versus 1.9 falls per week); however, this difference was not statistically significant due to the large number of patients who did not fall (approximately 40%) combined with the non-normal distribution in the number of falls among patients, both of which made statistical modeling and testing for falls difficult. Importantly, patients in the droxidopa group experienced fewer fall-related injuries (16.9% versus 25.6%) compared with patients in the placebo group.

Limitations of Study 306B

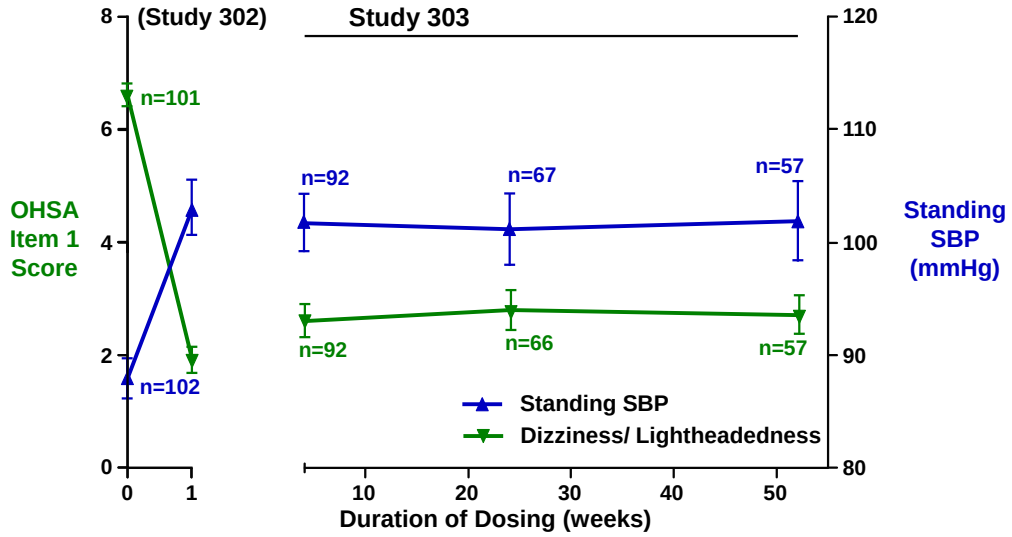
The primary analysis of the primary endpoint for Study 306B only included patients who completed both a Baseline visit (i.e., at time of Randomization), and a visit marking 1 week of maintenance therapy (i.e., at time of the primary endpoint). More patients receiving droxidopa than placebo (18 and 6, respectively) were excluded from the primary analysis because they dropped out of the study, with the large majority doing so during the forced dose-titration phase. Six of the 18 (33%) dropouts treated with droxidopa and 4 of the 6 (66%) dropouts treated with placebo were determined by Investigators to have discontinued because of a variety of AEs, with the remainder dropping out for a variety of reasons unrelated to AEs. The Sponsor determined it likely, in a *post-hoc* analysis, that all 6 (100%) placebo dropouts, and 9 of 18 (50%) droxidopa dropouts discontinued because of various AEs. To address the impact of missing data on the primary analysis, the Sponsor conducted a number of *post-hoc* sensitivity analyses using a range of assumptions and various imputation techniques. The results of these analyses support the study's overall conclusions. The Sponsor concludes that while missing data is a limitation of Study 306B, conclusions drawn from the primary analysis of this study nevertheless provide substantial evidence of the short-term efficacy of droxidopa.

Long-term Efficacy

While Chelsea has not confirmed a long-term clinical benefit for droxidopa, there are numerous data supporting durable benefits.

Study 303 was an open-label extension study designed to assess the long-term safety and efficacy of droxidopa; the great majority of patients entered Study 303 from Study 302 (see Section 6.2.1, Figure 6-40). In Study 303, improvements in OHSA Item 1 (dizziness/lightheadedness) and in standing SBP were consistent and durable with long-term droxidopa treatment (Figure 1-8). Improvements observed at Week 1 in both OHSA Item 1 and standing SBP were consistently maintained out to Week 52.

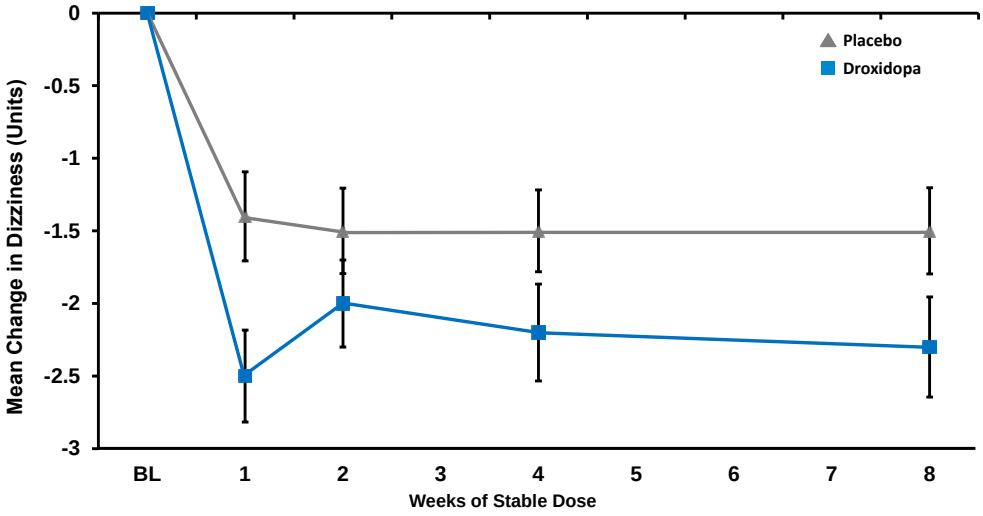
Figure 1-8 Study 303: Long-term Efficacy Results (MDE)



MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment; SBP=Systolic blood pressure.
Note: Baseline was the last non-missing value prior to the first dose of study drug as part of the lead-in study.

In Study 306, after 8 weeks of stable dose randomized double-blind treatment, treatment effects in favor of droxidopa were observed in the mean changes from Baseline in OHSA Item 1 (Figure 1-9) and standing SBP (Figure 1-10), although these differences were not statistically significant.

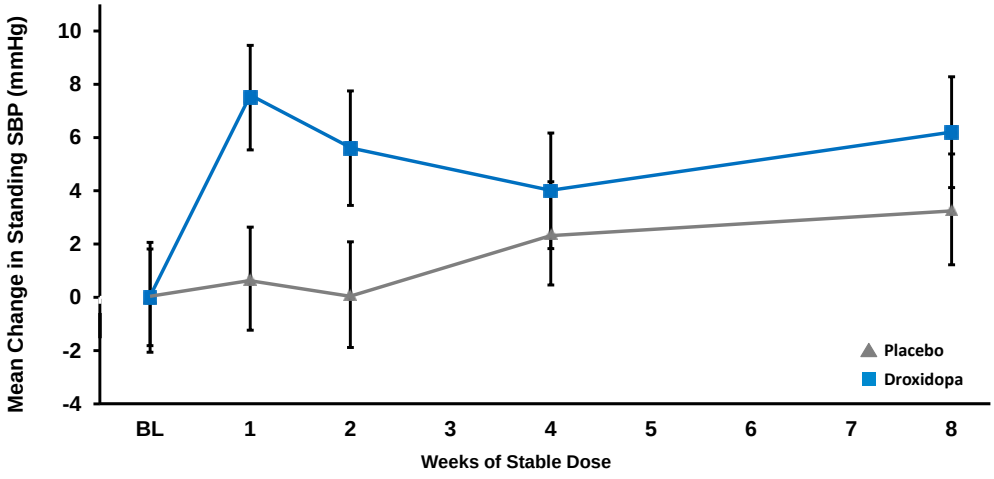
Figure 1-9 Study 306B+Interim Analysis Dataset: Long-term Efficacy: Dizziness at Weeks 1, 2, 4, and 8



p-value:	p=0.006	p=0.330	p=0.120	p=0.077
Placebo:	n=105	n=102	n=98	n=92
Droxidopa:	n=92	n=91	n=89	n=84

ANCOVA=analysis of covariance; BL=Baseline.
Note: Treatment difference for pooled studies tested using a parametric ANCOVA model with effects for treatment, Baseline value, and study.

Figure 1-10 Study 306B+Interim Analysis Dataset: Long-term Efficacy: SBP at Weeks 1, 2, 4, and 8



p-value:	p=0.007	p=0.077	p=0.872	p=0.276
Placebo:	n=105	n=102	n=98	n=92
Droxidopa:	n=90	n=91	n=86	n=84

ANCOVA=analysis of covariance; BL=Baseline; SBP=systolic blood pressure.
Note: Treatment difference for pooled studies tested using a parametric ANCOVA model with effects for treatment, Baseline value, and study.

In addition to these studies, Chelsea is currently conducting an additional randomized placebo-controlled study to confirm the findings generated thus far from the droxidopa development program. The proposed post-marketing study is discussed in Section 6.4.

Blood pressure

Multiple other studies and data from Chelsea-sponsored trials demonstrate large and statistically significant improvements in BP (Table 1-1).

While the BP analyses differ among these studies depending on their design, in all cases droxidopa clearly and consistently demonstrates a treatment effect on this important hemodynamic endpoint.

Table 1-1 Blood Pressure Analyses Across Droxidopa Studies

Study	Design	Endpoint	Improvement in SBP Following Droxidopa	p-value
Study 301	OL titration <2 weeks N=162	Δ standing SBP BL to EOT ~3 hours post dose	23.2 mmHg	p<0.001
Study 302	OL titration <2 weeks N=101	Δ standing SBP BL to EOT ~3 hours post dose	24.1 mmHg	p<0.001
Study 305	OL Crossover 1-3 months N=18	Δ24-hour mean SBP Off- vs. on-drug	7.3 mmHg	p=0.027
Study 102	Single-dose DB crossover Placebo vs. 600 mg vs. 2000 mg N=52	Δmean change supine SBP 3 hours post dose	placebo v 600 mg: 8.3 mmHg placebo v 2000 mg: 19.9 mmHg	p<0.001 p<0.001
DSP Study S10002	28 days DB treatment Placebo vs 300 mg TID N=121	Δorthostatic SBP decrease, 3 min tilt	11.6 mmHg	p=0.035
Mathias et al, 2001	10 weeks OL titration and treatment N=33	Δorthostatic SBP decrease 2 min post-standing, BL to final visit	17.7 mmHg	p=0.007
Freeman et al, 1999	Single dose DB crossover Placebo vs. 1000 mg N=10	Peak Δupright SBP (occurred at 5 hours post-dose)	27.9 mmHg	p<0.05

Δ=change; BL=Baseline; DB=double-blind; DSP=Dainippon Sumitomo Pharma Co., Ltd.; EOT=End of Titration; min=minute; OL=open-label; SBP=systolic blood pressure; TID=three times daily.

When all the data are considered, we conclude that the beneficial effects of droxidopa on BP are unequivocal.

SAFETY RESULTS

A total of 940 subjects have been treated with droxidopa in Chelsea and European DSP-sponsored studies; of these 940 subjects, 820 patients were included in Phase 2 and 3 clinical studies and 120 healthy volunteers were enrolled in Phase 1 studies. Across these studies, patients received doses of droxidopa ranging from 100 to 1800 mg/day. In the Phase 2 and 3 clinical studies, a total of 391 patients are estimated to have received at least 6 months of therapy, 263 patients at least 1 year of therapy, and 92 patients over 2 years of therapy with droxidopa. Droxidopa therapy was shown to be safe and well tolerated across multiple studies.

Table 1-2 lists fatal serious adverse events (SAEs), non-fatal SAEs, and the most common treatment-emergent adverse events (TEAEs) in the placebo-controlled studies.

Table 1-2 Summary of TEAEs in Studies 301/302 and Study 306 (Safety Sets)

	Study 301 and Study 302 (1-2 week RCT Phase)		Study 306 (8-10 Week RCT Phase)	
Preferred Term	**Placebo (N=132) n (%)**	**Droxidopa (N=131) n (%)**	**Placebo (N=108) n (%)**	**Droxidopa (N=114) n (%)**
Fatal SAEs	**0**	**0**	**0**	**0**
Non-Fatal SAEs	**1 (0.8)**	**0**	**4 (3.7)**	**5 (4.4)**
Patients with TEAEs Overall (%)	**31 (23.5)**	**30 (22.9)**	**87 (80.6)**	**91 (79.8)**
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Fatigue	3 (2.3)	2 (1.5)	6 (5.6)	8 (7.0)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)
Contusion	0	0	12 (11.1)	6 (5.3)
Excoriation	1 (0.8)	0	8 (7.4)	6 (5.3)
Oedema peripheral	2 (1.5)	0	6 (5.6)	5 (4.4)
Skin laceration	0	1 (0.8)	10 (9.3)	5 (4.4)
Blood pressure increased	0	0	7 (6.5)	4 (3.5)
Diarrhoea	1 (0.8)	1 (0.8)	8 (7.4)	4 (3.5)
Back pain	0	0	6 (5.6)	3 (2.6)
Fall[1]	9 (6.8)	1 (0.8)	1 (0.9)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

Note: Two deaths were not captured in the placebo-controlled study database: Patient 114002 (death occurred prior to completing Screening; Study 302); Patient 114003 (death occurred after 11 days after treatment discontinuation and was not entered into study database, Study 302). Information on all deaths can be found in Section 7.4.2 and in Table 7-13.

1 In Study 306 Investigators were instructed not to record a fall as an AE.

Cardiovascular Safety

When considering the elderly and frail condition of the average nOH patient, it is particularly noteworthy that there is no evidence of a cardiovascular safety signal (Section 7.5.3) seen in the efficacy studies (Studies 301, 302, and 306) or the safety studies (Studies 102, 303, 304, and 305). For example, no cardiovascular-related TEAEs were reported during the randomized treatment phases of Studies 301 and 302. In Study 306, in the droxidopa group 1 patient (0.9%) each reported single TEAEs of atrial fibrillation (considered an SAE), sinus bradycardia, supraventricular extrasystoles, tachycardia, and tachycardia paroxysmal, while in the placebo group 1 patient (0.9%) each reported single TEAEs of sinus bradycardia, tachycardia, and chest discomfort.

During the long-term extension studies, 32 patients (7.6%) reported TEAEs in the Cardiac Disorders System Organ Class (SOC), 7 patients (1.7%) reported cardiac-related TEAEs in the General Disorders and Administration Site Conditions SOC, and 6 patients (1.4%) reported cardiac-related TEAEs in the Vascular Disorders SOC.

Given the importance of establishing the cardiovascular safety of droxidopa, all cardiovascular SAEs (both fatal and non-fatal) as well as cardiovascular AEs leading to discontinuation were adjudicated by an independent expert in the field. This expert found no evidence that droxidopa is associated with an increase in the number of cardiovascular SAEs.

Supine Hypertension

The incidences of supine hypertension and TEAEs resulting from increased BP were relatively low. Droxidopa does appear to increase the incidence of these types of TEAEs in this population. Additional analyses and information on hypertension can be found in Section 7.5.2. For example, overall rates of supine hypertension (defined as SBP >180 mmHg at all supine measurements during the Orthostatic Standing Test [OST]) were higher in the droxidopa group compared with the placebo group in the randomized treatment phase of Studies 301/302 integrated (droxidopa: 3.1%; placebo: 1.5%) and Study 306 (droxidopa: 7.9%; placebo: 4.6%). Of note, Study 305, a dedicated 24-hour ambulatory BP monitoring study, showed no difference in the increase in nocturnal (supine) compared with diurnal BPs while on droxidopa.

Overall, and especially when considering the advanced age and complications of the underlying diseases in the study population, droxidopa had a favorable safety profile in the long-term extension studies, which included 422 patients with an average exposure of approximately 1 year.

Full details on patient deaths (Section 7.4.2), SAEs (Section 7.4.3), common TEAEs (Section 7.4.1), and TEAEs leading to discontinuation (Section 7.4.4) can be found throughout this Briefing Document.

SUMMARY BASIS FOR APPROVAL

Summary of Benefits

The collective data from the Sponsor's clinical development program demonstrate that droxidopa is effective for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

Study 301 conclusively demonstrates the efficacy of droxidopa, and Study 306B provides independent substantiation of these results. The overall data from these 2 adequate and well-controlled, multi-center, double-blind, randomized induction design studies demonstrate that droxidopa provides clear and consistent short-term benefits for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN. These data are supported by secondary data from an additional randomized, double-blind, placebo-controlled withdrawal design study. Short-term effectiveness was demonstrated across a range of symptoms and pharmacodynamic measures including improvements in dizziness/lightheadedness/syncopal symptoms, the cardinal symptom of nOH; increases in standing BP; and global improvements as assessed by clinicians (Clinical Global Impression-Severity [CGI-S] and Clinical Global Impression-Improvement [CGI-I]). There was also a strong suggestion of a reduction in falls and fall-related injuries (Study 306B).

Results from long-term studies (Study 303 following up to 12 months of open-label treatment and Study 306 following up to 2 months of double-blind treatment) provide suggestive evidence that the benefits of droxidopa on both symptoms and standing BP are durable.

To confirm the long-term efficacy of droxidopa, Chelsea is conducting a large, 450 patient randomized-controlled study (intended for post-marketing) to confirm the findings generated thus far from the droxidopa development program.

Summary of Risks

The droxidopa safety database is large relative to the population of patients diagnosed with this Orphan Drug condition, and demonstrates that droxidopa is safe and well tolerated. The overall incidence of TEAEs was similar between droxidopa and placebo in placebo-controlled studies. Droxidopa treatment was associated with a small increase in the incidence of headaches, dizziness, nausea, and hypertension. Most TEAEs were mild to moderate in severity, and events were generally considered by the Investigators to be unlikely or not related to study drug. Longer-term studies were not associated with a change in the incidence or types of TEAEs observed in the short-term trials.

Droxidopa modestly increases the incidence of supine hypertension and BP-related TEAEs in this population and not to severe levels in most instances. However, the overall incidence of cardiovascular-related TEAEs experienced by patients treated with droxidopa was low. A dedicated 24-hour ambulatory BP monitoring study showed no difference in the increase on drug versus off drug in nocturnal (supine) compared with diurnal BPs. The risk of supine hypertension can be addressed with appropriate patient selection, BP monitoring, and labeling. The results of a thorough clinical QT/QTc study indicate that droxidopa has no effect on cardiac repolarization or other atrial or ventricular conduction parameters.

Droxidopa data from clinical studies as well as a large post-marketing safety database in Japan, where the drug has been approved for over 20 years, further supports the safety of droxidopa for the treatment of nOH.

Conclusion

Symptomatic nOH is a debilitating condition for which there exists a significant unmet medical need. Droxidopa is the only agent to have demonstrated, in adequate and well-controlled trials, improvements in the acute signs and symptoms of nOH. Droxidopa has been shown to be generally safe and well tolerated in this patient population, which includes a large subgroup of patients with co-existing cardiac morbidities. There is a small increase in the incidence of supine hypertension associated with droxidopa therapy. The totality of data from the Sponsor's clinical development program, including those collected during 2 randomized, placebo-controlled induction design studies and multiple other supportive studies, demonstrates that droxidopa is safe and effective for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition/Term
3-OM-DOPS	3-O-Methyl-DOPS
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BE	Bioequivalence
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRO	Contract Research Organization
COMT	Catechol-o-methyltransferase
CYP	Cytochrome P
DβH	Dopamine Beta Hydroxylase
DBP	Diastolic Blood Pressure
DCRP	Division of Cardiovascular and Renal Products
DDC-I	DOPA Decarboxylase Inhibitor
DHPG	Dihydroxyphenylglycol
DMC	Data Monitoring Committee
DOPA	3,4-Dihydroxyphenylalanine
DSP	Dainippon Sumitomo Pharma Co., Ltd.
ECG	Electrocardiogram
ETV	Early Termination Visit
FAP	Familial Amyloid Polyneuropathy
FAS	Full Analysis Set
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
HC	3,4-Dihydroxytoluene

Abbreviation	Definition/Term
HMPG	3-Methoxy-4-hydroxy-phenylglycol
HR	Heart Rate
IND	Investigational New Drug
ITT	Intent-to-Treat
IV	Intravenous
LD_{50}	Dose required to kill 50% of the animals
LOCF	Last Observation Carried Forward
MAO	Monoamine Oxidase
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MID	Minimally Important Difference
mITT	Modified Intent-to-Treat
MHPG	Methoxy-4-hydroxyphenylglycol
MMRM	Mixed Model Repeated Measures
MSA	Multiple System Atrophy
NDA	New Drug Application
NDAN	Non-Diabetic Autonomic Neuropathy
NE	Norepinephrine
NMS	Neuroleptic Malignant Syndrome
nOH	Neurogenic Orthostatic Hypotension
OH	Orthostatic Hypotension
OHDAS	Orthostatic Hypotension Daily Activity Scale
OHSA	Orthostatic Hypotension Symptom Assessment
OHQ	Orthostatic Hypotension Questionnaire
OND	Office of New Drugs
OST	Orthostatic Standing Test
PA	Protocatechuic Acid
PAF	Pure Autonomic Failure
PD	Parkinson's Disease
PK	Pharmacokinetic
PRO	Patient-reported Outcome
QTc	QT interval corrected
RBC	Red Blood Cell
RCT	Randomized-Controlled Treatment
SAE	Serious Adverse Event

Abbreviation	Definition/Term
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SEALD	Study Endpoints And Labeling Development
SOC	System Organ Class
SPA	Special Protocol Assessment
TEAE	Treatment-emergent Adverse Event
TID	Three times daily
T_{max}	Time to maximum plasma concentration
US	United States

1. PRODUCT DEVELOPMENT RATIONALE

This briefing document summarizes data in support of New Drug Application (NDA) 203202, for NORTHERA™ (Droxidopa) 100 mg, 200 mg, and 300 mg oral capsules. This application is sponsored by Chelsea Therapeutics, Inc. (Chelsea), located in Charlotte, NC.

1.1 Proposed Indication, Dosage, and Administration

1.1.1 Proposed Indication

Chelsea is proposing the following indication for the package insert for NORTHERA (droxidopa) Capsules:

NORTHERA is indicated for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in adult patients with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)], Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN). The clinical benefits of NORTHERA are improvements in dizziness, lightheadedness, feeling faint, or "feeling like you might black out." Clinical benefit has been demonstrated in short-term trials; long-term benefits have not been verified.

1.1.2 Proposed Dosage and Administration

The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily (TID): upon arising in the morning; midday; and late afternoon at least 3 to 4 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Patients should take NORTHERA consistently either with food or without food. Dose optimization should be based on a patient's symptomatic response and clinical condition. The dose may be increased in increments of 100 mg TID every 24 to 48 hours up to a maximum dose of 600 mg TID (i.e., a maximum total daily dose of 1800 mg).

Dose optimization should be based on a patient's symptomatic response after at least one full day on therapy. During clinical trials, dose optimization was usually conducted on a daily basis and completed within a 10 day period. Supine BP should be monitored regularly and more frequently when changing dose. The dose of NORTHERA should be reduced or administration stopped if supine BP increases excessively. The last dose should be taken at least 3-4 hours before bedtime.

Patients who miss a dose of NORTHERA should take their next scheduled dose. Patients should not take more than the prescribed total daily amount of NORTHERA in any 24-hour period.

Of note, in each of the Phase 3 studies (i.e., Studies 301, 302, and 306) all patients entered a dose titration/optimization period, where their doses were titrated to effect prior to entry into the treatment period of the study. Details regarding the dose titration periods are provided in Section 6.1.1 for Studies 301 and 302 and in Section 6.1.2 for Study 306.

1.2 Background for Development

1.2.1 Introduction

Orthostatic hypotension (OH) is a reduction in standing systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes of standing. It is a physical sign and not a disease (Consensus Statement, 1996). nOH is a subtype of OH and specifically results from a failure of the autonomic nervous system to respond appropriately to changes in posture, resulting in hypotension upon standing. This is in marked contrast to OH, which can result from volume depletion, dehydration, and vasodilatation, and is not associated with dysfunction of the autonomic nervous system.

1.2.1.1 Diseases and Conditions Associated with nOH

nOH is caused by a variety of neurodegenerative conditions (PD, MSA, PAF), NDAN, and congenital neurological disorders, occurs in approximately 80,000 patients in the United States (US [Colosimo et al, 1995]) and is, therefore, considered an Orphan Disease population. Some of these disorders affect peripheral autonomic neurons exclusively (e.g., PAF, DβH Deficiency, and NDAN) while others (MSA and PD) affect both autonomic and motor neurons. Despite the heterogeneity in the overall nOH patient population, the disorders associated with this condition all share a common pathophysiology, which is an inadequate norepinephrine (NE) response from sympathetic vasomotor neurons, resulting in autonomic failure and generalized blood pressure (BP) dysregulation (Freeman et al, 2011). As a result, these patients often experience both hypotension upon standing as well as hypertension when lying down.

1.2.1.1.1 Symptomatic nOH is a Debilitating Condition

Symptomatic nOH is a severely debilitating condition that can substantially reduce a patient's quality of life, and is associated with an increased risk of mortality, stroke, and myocardial ischemia. Dizziness, which characteristically presents as lightheadedness, or presyncope, is the cardinal symptom of nOH and results from cerebral hypoperfusion upon standing (Mathias et al, 1999) due to an inadequate release or utilization of NE from the sympathetic vasomotor neurons, leading to limited vasoconstriction and a decrease in BP upon assuming an upright posture. Patients may also experience syncope or lose consciousness and fall, greatly increasing the risk of significant physical injury including hip fracture and head trauma (Goldstein and Sharabi, 2009), factors that contribute to morbidity, disability, or death (Lahrmann et al, 2006). Fear of these types of injuries can result in patients limiting their activities, which leads to a host of complications ranging from a reduction in muscle mass and overall fitness to depression, feelings of social isolation, and loss of independence (Vellas et al, 1997; Sclatter and Alagiakrishnan, 2004). Taken together, the symptomatic consequences of nOH can substantially reduce patients' quality of life (Mathias, 2008; Maule et al, 2007; Magerkurth et al, 2005).

In addition to the complications associated with cerebral hypoperfusion upon standing, patients with nOH are at risk of developing supine hypertension. It has been demonstrated that more than 50% of patients with autonomic failure experience hypertension when supine (Shannon et al, 1997; Shibao et al, 2006). Supine hypertension causes hypertensive heart disease (Maule et al, 2006), brain ischemia and hemorrhage (Sandroni et al, 2001), papilloedema, and hypertensive

retinopathy (Maule et al, 2007). Left ventricular hypertrophy has been associated with supine hypertension in patients with primary autonomic failure (Vagaonescu et al, 2000). Elevated nighttime SBP is independently and significantly associated with cardiovascular mortality (Pathak et al, 2004). Furthermore, nighttime pressure natriuresis and the resulting volume depletion can exacerbate symptoms associated with nOH (Jordan et al, 1999).

As a result of the range of problems that are attributed to autonomic failure, the prognosis and overall clinical outcome of patients with nOH is poor. In a 1-year observation study of 31 patients with autonomic failure and 26 age-matched PD patients without autonomic failure, 5 of the 31 patients (16.1%) with autonomic failure died during the 1-year observation period compared with none of the age-matched PD patients without autonomic failure (Pathak et al, 2005). Other longitudinal studies have also shown that chronic OH increases the risk of mortality (Raiha et al, 1995; Davis et al, 1987; Masaki et al, 1998).

1.2.2 Therapeutic Goal for nOH

The therapeutic goal for nOH is to decrease the incidence and severity of postural symptoms rather than restore normotension (Maule et al, 2007); however, it is still important that any therapy for the treatment of symptomatic nOH specifically increase standing BP without substantially increasing supine BP.

1.2.3 Current Treatments for nOH

1.2.3.1 Non-Pharmacologic Therapy

Non-pharmacologic therapies are generally the first step in the treatment of nOH, and include patient education, exercise, physical counter-maneuvers, use of abdominal binders or elastic stockings, and modifying dietary habits such as increasing sodium and fluid intake. Over time, these measures frequently become ineffective and patients generally progress to pharmacological therapies. Furthermore, these non-pharmacological measures are associated with poor patient compliance.

1.2.3.2 Pharmacologic Therapy

1.2.3.2.1 FDA Approved Treatment

Midodrine is the only medication approved by the Food and Drug Administration (FDA) for the treatment of symptomatic OH. It is a synthetic sympathomimetic amine, which is a peripheral, selective, direct alpha-1-adrenoreceptor agonist (McTavish and Goa, 1989; Robertson and Davis, 1995). The indiscriminate pressor effect of midodrine is due to both arterial and venous constriction. Midodrine was granted accelerated approval based on an increase in SBP at 1 minute upon standing used as a surrogate endpoint for symptomatic benefit. However, while BP is important in the pathophysiology of nOH, it is not validated as a surrogate endpoint for therapeutic (i.e., clinical) benefit and is no longer considered an acceptable primary endpoint by the Division of Cardiovascular and Renal Products (DCRP).

Despite showing a clear increase in standing SBP, midodrine failed to show statistically significant benefits on symptomatic endpoints at the time of approval. To date, no studies have been conducted which demonstrate midodrine improves the symptoms of nOH.

The use of midodrine has significant limitations. Midodrine has a black box and bolded warning indicating that marked elevation of supine SBP >200 mmHg was seen in 13.4% of patients administered 10 mg (i.e., the recommended dose). Since supine hypertension occurs as part of nOH, midodrine has the potential to exacerbate this condition in some patients, putting them at further risk for cardiovascular events. Midodrine is also contraindicated for patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma, or thyrotoxicosis.

In the droxidopa clinical trials, roughly 30% of patients had previously been taking midodrine. This suggests that there remains a large unmet medical need for treatments in addition to midodrine for patients with symptomatic nOH.

1.2.3.2.2 Non-FDA Approved Treatments for nOH

Agents not approved for the treatment of nOH are frequently used in patients with symptoms as monotherapy or in combination with other treatments. These include, but are not limited to: volume-expanding agents (e.g., fludrocortisone), vasoconstricting agents (e.g., pseudoephedrine/ephedrine), desmopressin, acetylcholinesterase inhibitors (e.g., pyridostigmine), and erythropoietin. Each of these non-approved agents is associated with limited effectiveness along with potentially serious side effects.

2. NONCLINICAL

2.1 Overview of Nonclinical Studies

Nonclinical studies have been completed with droxidopa to evaluate the drug's pharmacodynamic activity (including mechanism of action studies, primary and secondary pharmacology, safety pharmacology studies), pharmacokinetic (PK) profile (absorption, distribution, metabolism, excretion, and toxicokinetic studies), local and systemic adverse effects (repeat-dose toxicity studies), potential to damage genetic material (genotoxicity studies), carcinogenic hazard, and effects on reproduction and the development of offspring (reprotoxicity studies) following oral dose administration.

Non-clinical pharmacology studies demonstrated that droxidopa increased both BP and heart rate (HR) in rats and that these effects were a result of droxidopa's metabolic conversion to NE. Pharmacology studies also demonstrated that droxidopa is able to cross the blood-brain barrier and increase NE concentrations in the brain. Results of PK studies in several animal species reported that the half-life of droxidopa ranges from 1.3 hours in dogs to 4.2 hours in rats. The bioavailability of the drug in rats ranged from 65% to 90%. Higher concentrations of droxidopa are found in the kidneys and liver compared with other tissues in all species studied. The major metabolite identified in serum, urine, and tissue was 3-O-Methyl-DOPS (3-OM-DOPS). There was no evidence of biotransformation of droxidopa into any of its other 3 stereoisomers.

A full program of toxicology testing was undertaken to support clinical testing. In acute oral toxicity studies, the dose required to kill 50% of the animals (LD_{50}) in mice and rats was greater than 10,000 mg/kg. The results of repeat-dose toxicology studies in rats and mice revealed some evidence of cardiac and renal toxicity that was consistent with increased sensitivity of these species to the effects of NE. The cardiac and renal changes were considered exacerbations of spontaneous age-related degenerative changes in rats and mice, which were not observed in either dogs or monkeys. There was no evidence that droxidopa was genotoxic or carcinogenic in animals. Reproductive toxicity and teratogenicity studies revealed that droxidopa did not affect fetal development or reproductive function at the doses tested. In some animal studies, distribution in the milk supply and inhibition of the growth of the young during the period in which the drug was administered to the nursing dam has been reported.

3. CLINICAL PHARMACOLOGY

A brief summary of the clinical pharmacology profile of droxidopa is provided below; a more detailed discussion is provided in Appendix 1 (Section 10.1).

3.1 Mechanism of Action

The exact mechanism of action of droxidopa in the treatment of nOH is unknown. Droxidopa is a synthetic amino acid analog that is directly metabolized to NE by dopa-decarboxylase, which is extensively distributed throughout the body. Droxidopa exerts its effects through NE and not through the parent molecule or other metabolites. Norepinephrine increases BP by inducing peripheral arterial and venous vasoconstriction. Droxidopa in humans induces relatively small transient rises (less than 1 ng/mL) in plasma NE. Droxidopa crosses the blood-brain barrier and may affect the central as well as the peripheral autonomic nervous system.

3.2 Pharmacokinetics

3.2.1 Absorption

After oral dosing with droxidopa capsules in healthy elderly volunteers, droxidopa is rapidly absorbed. Peak droxidopa blood concentrations were reached between 1 and 4 hours post-dose (mean of approximately 2 hours) with a mean droxidopa half-life of approximately 2.5 hours. Increasing doses of droxidopa between 100 and 2000 mg result in increases in AUC (area under the plasma concentration time curve) and C_{max} (maximal plasma concentration).

Food Effect: In healthy subjects, high fat meals reduced systemic exposure to droxidopa (as measured by AUC) by 20% and the peak blood concentration C_{max} by 35%. C_{max} was delayed by 2 hours compared to fasting; half-life was not affected.

3.2.2 Distribution

Droxidopa is known to cross the blood brain barrier in both animals and humans. Serum protein binding is inversely concentration dependent (75% to 25%) over the range of 0.1 mcg/mL to 10 mcg/mL. The apparent volume of distribution at steady state is approximately 200 L (estimated) which is evidence of extra plasma distribution.

3.2.3 Metabolism

Droxidopa is metabolized in humans and animals into 3 initial metabolites (NE, 3-OM-DOPS, and protocatechualdehyde), with 3-OM-DOPS being the primary metabolite. After dosing in humans, plasma NE levels peak within 3 to 4 hours and are generally low (less than 1 ng/mL). Droxidopa is initially converted to 3-OM-DOPS by catechol-O-methyltransferase (COMT), to NE by 3,4-dihydroxyphenylalanine (DOPA) decarboxylase, or to protocatechualdehyde by DOPS aldolase.

Norepinephrine is the active metabolite of droxidopa. Although there was generally a small increase in NE with escalating doses of droxidopa, the variability was high and the dose relationship was not consistent. While the other major metabolites of droxidopa (3-OM-DOPS, protocatechualdehyde, and vanillic acid [a metabolite of 3-OM-DOPS]) may have some

vasomotor activity, their contribution is considered minor as they do not appear to significantly influence the pharmacodynamic effect of droxidopa.

3.2.4 Excretion

In animals, renal clearance of radioactive label was approximately 75%, including parent drug (15%), and the major metabolites; 3-OM-DOPS (6%-15%), protocatechualdehyde (10%-20%), and vanillic acid (2%-11%). In humans, renal clearance of parent drug and major metabolites was similar to animals.

3.2.5 Population Pharmacokinetics

A population PK analysis was conducted in Study 302 (for study design details, see Appendix 2; Section 10.2.3). Concurrent administration of levodopa (including a DOPA decarboxylase inhibitor [DDC-I]) was associated with a 2-fold increase in drug exposure (AUC) and a 50% increase in exposure to 3-OM-DOPS.

Increasing age was associated with an increase in exposure (AUC) to both drug and 3-OM-DOPS. The increase was approximately 0.8% per year of age for droxidopa and 1.8% per year of age for 3-OM-DOPS. Exposure to droxidopa and 3-OM-DOPS was not affected by body size (weight, height, and body mass index [BMI]) or gender. Hepatic function (assessed by aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase, and total bilirubin) did not influence exposure to drug.

3.3 Pharmacodynamics

Peak droxidopa plasma concentrations are associated with peak increases in SBP and DBP. Droxidopa has no clinically significant effect on standing or supine HRs in patients with autonomic failure.

3.3.1 Cardiac Electrophysiology

No prolongation of the QT interval corrected (QTc) was observed with droxidopa at single oral doses up to 2000 mg, as shown in a dedicated thorough electrocardiography study which included both placebo and positive control (moxifloxacin) arms (Study 102; for study design details, see Appendix 2; Section 10.2.8).

4. OVERVIEW OF THE DROXIDOPA CLINICAL DEVELOPMENT PROGRAM

4.1 Chelsea-Sponsored Studies

During the droxidopa clinical development program, the Sponsor conducted 10 clinical studies enrolling a total of 666 unique patients with symptomatic nOH, 631 of whom were treated with droxidopa (see Section 7.2.2). A summary of these 10 studies, including 2 pivotal Phase 3 randomized, placebo-controlled, induction design studies that measured short-term safety and efficacy of droxidopa, an additional supportive short-term placebo-controlled withdrawal design study, and 7 other supportive studies can be found in Table 4-1. Detailed descriptions of the design of each study as well as tabular summaries of each study's patient population characteristics, study objectives, endpoints, and results are provided in Appendix 2; Section 10.2.

Of note, in each of the 2 pivotal studies, all patients entered a dose titration/optimization period where their dose was titrated to effect based on individualized efficacy and safety responses. In Study 301 [see Section 6.1.1] dose titration was conducted before randomization and was open-label. In Study 306B [see Section 6.1.2], dose titration was conducted after randomization during the double-blind phase.

The original NDA (28 September 2011) included data from the following studies: completed Studies 301, 302 303, 305, 101, and 102 as well as interim data from Study 304, which was ongoing at the time of the original submission, and top-line safety data from Study 306A (Interim Analysis Dataset). The current droxidopa NDA (14 August 2013) included data from all completed studies summarized in Table 4-1.

Table 4-1 List of Chelsea-Sponsored Studies

Study Number	Study Title	Number of Patients	Design
Pivotal Phase 3 Clinical Studies (n=2)			
Study 301	A Multi-Center, Double-Blind, Randomized, Placebo Controlled, Parallel-Group, Induction-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension	N=263 – Safety (entered open-label titration) N=162 – Efficacy (randomized and treated)	Induction design. Up to 2-week open-label titration followed by 1-week open-label washout, followed by 1-week double-blind treatment period.
Study 306B	A Multi-Center, Double-Blind, Randomized, Parallel Group, Placebo Controlled Study to Assess the Clinical Effect of Droxidopa in the Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Patients with Parkinson's Disease	N=171 – Safety (randomized into double-blind titration and dosed with study drug) N=147 – Efficacy (treated and reported OHSA Item 1 at Week 1)	Induction design. Up to 2-week double-blind titration followed by 8-week double-blind treatment period.

Table 4-1 List of Chelsea-Sponsored Studies

Study Number	Study Title	Number of Patients	Design
Supportive Clinical Studies (n=8)			
Study 302	A Multi-Center, Double-Blind, Randomized, Placebo Controlled, Parallel-Group, Withdrawal-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension	N=181 – Safety (entered open-label titration) N=101 – Efficacy (randomized and treated)	Withdrawal design. Up to 2-week open-label titration followed by 1-week open-label treatment, followed by 2-week double-blind withdrawal period.
Study 303	A Multi-Center, Open-Label Study With a Two-Week Randomized, Placebo-Controlled Withdrawal Period to Assess the Long-Term Safety and Clinical Benefit of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension	N=102 – Safety (treated with study drug) N=75 – Efficacy (treated and randomized into 2-week withdrawal period following 3 months of open-label treatment)	Withdrawal design and long-term extension study. Three-month open-label treatment period followed by 2-week double-blind withdrawal period, followed by open-label long-term extension treatment.
Study 304	A Multi-Center, Open-Label Study To Assess the Long-Term Safety of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension	N=350	Long-term extension study. Open-label long-term extension, safety only study.

Table 4-1 List of Chelsea-Sponsored Studies

Study Number	Study Title	Number of Patients	Design
Study 305	A Multi-Center, Open-Label, Study to Assess the Effect of Droxidopa on 24-Hour Blood Pressure Profile in Subjects with Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-Diabetic Neuropathy and Symptomatic Orthostatic Hypotension	N=18	Dedicated ambulatory BP monitoring study. Patients 24-hour average BP measured both off and on drug.
Study 306A (also called 306 Interim Analysis Dataset)	A Multi-Center, Double Blind, Randomized, Parallel -Group, Placebo Controlled Study to Assess the Clinical Effect of Droxidopa in the Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Patients with Parkinson's Disease	N=51	Induction design. Up to 2-week double-blind titration followed by 8-week double-blind treatment period.
Study 101	A Randomized, Open-Label, Three-Period, Three-Sequence, Single-Dose Crossover and Separate Three-Daily-Dose Treatment Period Study Comparing the Pharmacokinetic Profiles Following Oral Dosing of 300 mg of Droxidopa in the Fed versus Fasted State, the Bioequivalence of Three 100 mg Capsules of Droxidopa versus a Single 300 mg Capsule of Droxidopa, and 300 mg of Droxidopa Given Three Times at Four Hour Intervals in Healthy, Elderly Subjects	N=24	BE Study. Study of PK for TID dosing, fed/fast effect on PK, comparative PK of 300mg dose.
Study 102	A Double-Blind, Randomized, Crossover Trial to Define ECG Effects of Droxidopa Using a Clinical and a Supratherapeutic Dose Compared with Placebo and Moxifloxacin (a Positive Control)in Healthy Men and Women: A Thorough ECG Trial	N=52	Dedicated thorough QTc study.
Study 104	A Randomized, Open-Label, Bioequivalence Study of One 100 mg and One 200 mg Capsule of Droxidopa Versus One 300 mg Capsule of Droxidopa in Healthy Subjects	N=24	A PK study comparing the BE of 300 mg capsules with 100+200 mg capsules.

4.2 DSP-Sponsored Studies

Chelsea licensed the data rights from Dainippon Sumitomo Pharma Co., Ltd. (DSP) to aid in the development of droxidopa in the US in 2006. DSP conducted studies in both Japan and Europe during their development of droxidopa, and these data were included in the original NDA. Efficacy data from these trials are not discussed in this Briefing Document (exposure data are discussed briefly in Section 7.2.1).

4.2.1 European Studies

Data from 6 studies sponsored by DSP that were conducted in Europe were included in the original NDA to provide additional information regarding droxidopa. The European studies included 2 placebo-controlled European Phase 2 studies (2034 [N=37] and S10002 [N=121]). The data from these studies support the conclusion that droxidopa is safe and that it improves BP in nOH patients as measured by absolute standing SBP and by the decrease in the drop in SBP upon standing. Each of these studies had its own open-label, long-term follow-up study with treatment of up to 2 years with droxidopa.

4.2.2 Japanese Studies

Droxidopa was approved in Japan in 1989 for the treatment of OH, syncope, and dizziness on standing up in Familial Amyloid Polyneuropathy (FAP) and Shy-Drager Syndrome (i.e., MSA), and for the treatment of freezing phenomenon and dizziness on standing up in PD. In 2000, this approval was expanded to include the alleviation of vertigo, staggering, dizziness on standing up, lassitude, and weakness in hemodialysis patients with OH.

The Japanese studies included 2 large placebo-controlled studies (E5 [N=226], E26 [N=97]) and 24 additional open-label studies.

4.3 Challenges of Study Design

The incidence of symptomatic nOH from non-diabetic neurological diseases, including PD, MSA, PAF, NDAN, and DβH Deficiency, is relatively low and meets the definition of an Orphan Disease. As with all orphan indications, enrolling a sufficient number of patients into clinical trials is challenging. To address this, Chelsea opened enrollment in Studies 301 and 302 to a heterogeneous population of patients with nOH, a variety of autonomic dysfunction disorders, and multiple comorbidities. Of note, Chelsea did not study patients with diabetic autonomic neuropathy given the inherent risks of administering a NE pro-drug to patients with comorbidities of hypertension and poor glucose control.

Because patients with symptomatic nOH might respond differently to study medication given different severities and disease etiologies, an individualized dose-titration strategy was employed in an attempt to optimize the dose of droxidopa for each patient (details regarding the dose titration periods are provided in Section 6.1.1 for Studies 301 and 302 and in Section 6.1.2 for Study 306). Patients' doses were titrated from 100 to 600 mg TID in 100 mg increments. To increase the likelihood of determining a treatment effect, only patients determined to have a response (based on pre-specified improvements in both dizziness and BP) to droxidopa in the titration phase were enrolled into the randomized-controlled phase of each respective study.

At the time of the initiation of Chelsea's studies, there were no successful development programs or widely accepted study designs that could be used to inform Chelsea on the optimal development of droxidopa to fulfill the Agency's mandate of demonstrating a symptomatic benefit with droxidopa. In addition, some clinical experts in the field suggested that it would be difficult to enroll and keep enrolled the most severely ill patients in longer placebo-controlled trials, thereby making it difficult to demonstrate droxidopa has a durable clinical benefit in a placebo-controlled setting. Given this landscape, and in agreement with the Agency, Chelsea initially conducted 2 short-term clinical trials: Studies 301 and 302, and measured durability using a randomized-withdrawal period within the long-term extension Study 303.

Study 301 was granted a Special Protocol Assessment (SPA) by the Agency. The intent of the short-term placebo-controlled periods was to maximize the likelihood that patients most severely affected by symptomatic nOH would be enrolled into the trials as well as to maximize the statistical power for each study.

4.4 Study Endpoints

4.4.1 Symptomatic Endpoints

While BP is clearly important in the pathophysiology of nOH and has been traditionally utilized as an endpoint in other nOH clinical trials, it is not validated as a surrogate endpoint of therapeutic (i.e., clinical) benefits and is no longer considered an acceptable primary endpoint by the DCRP. Given these concerns, the Agency required the use of symptomatic endpoints at the beginning of the droxidopa development program to establish efficacy.

Orthostatic Hypotension Questionnaire (OHQ)

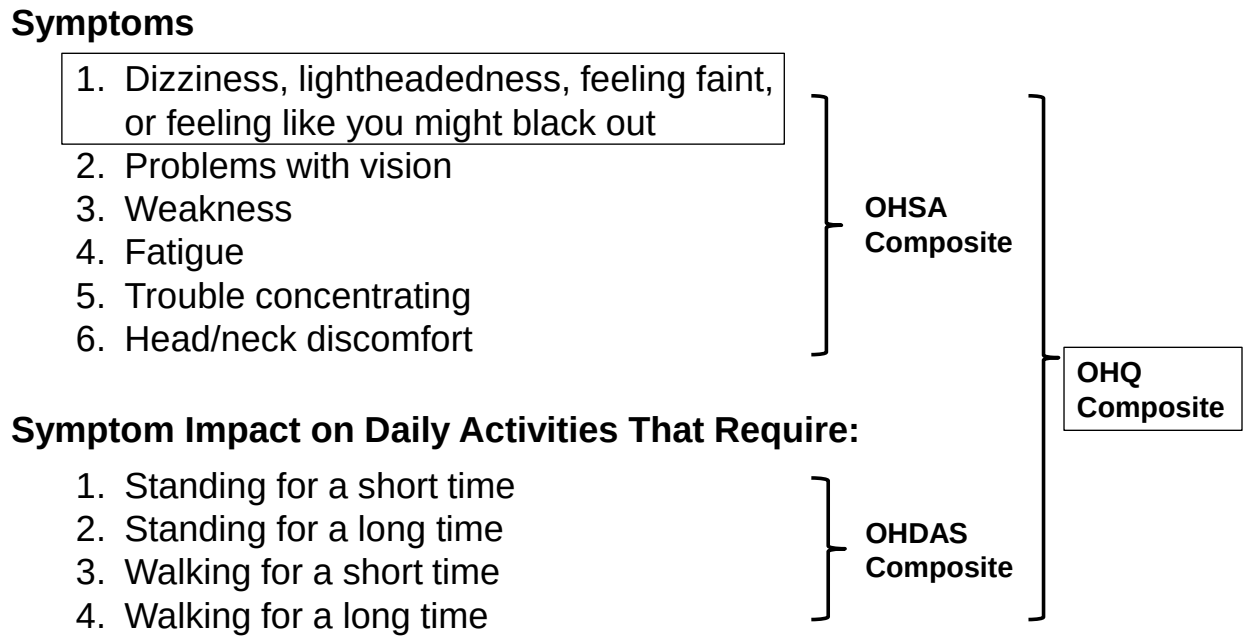
The OHQ is a patient-reported symptomatic endpoint and is the only validated scale for the study of therapeutic intervention in nOH (Kaufmann et al, 2012). The OHQ is composed of 10 individual items: 6 items measure specific symptoms (orthostatic hypotension symptom assessment [OHSA]), and 4 items measure the impact of those symptoms on a patient's daily activities (Orthostatic Hypotension Daily Activities Scale [OHDAS]; Figure 4-1). For the OHSA, patients are instructed to rate, using a 0 to 10 point Likert scale (0 meaning 'not experienced' and 10 meaning "worst possible"), how severe their symptoms from low BP had been *on average over the past week;* the OHSA composite score is the average of the 6 individual symptom scores on a scale of 0 to 10. For the OHDAS, patients are instructed to rate from 0 (no interference) to 10 (complete interference) how the symptoms of nOH they experienced affected their daily life *on average over the past week*; the OHDAS composite score is the average of the 4 individual symptom impact scores on a scale of 0 to 10. The OHQ composite score (calculated as the average, on a scale of 0 to 10, of the OHSA and OHDAS composite scores) allows for a holistic summary of benefits experienced by the patient. Decreases in individual and composite scores represent improvements. Of note, the OHQ composite score and specific items of the OHQ were used in the midodrine development program.

The Sponsor previously concentrated on the composite score of all 10 OHQ items as a primary measure of efficacy in Studies 301 and 303. Dizziness, lightheadedness, feeling faint, or feeling like you might black out upon standing are the cardinal symptoms of symptomatic nOH and are captured as part of the OHSA Item 1 question. OHSA Item 1 has been identified by the FDA's Study Endpoints and Label Development (SEALD) group as representing the core symptoms of nOH, and providing the best measurement of disease-defining symptoms of nOH. SEALD provided the following comment regarding OHSA Item 1 in the FDA Briefing Document for the first Cardiovascular and Renal Drugs Advisory Committee:

"The OHSA Item 1, however, captures the most important symptoms of the patients who suffer from symptomatic orthostatic hypotension: dizziness, lightheadedness, feeling faint, or 'feeling like you might black out.' The concept of OHSA Item 1 is comprehensive and unambiguous. The symptom assessed by this item is a core symptom of symptomatic neurogenic orthostatic hypotension as assessed by the qualitative research and therefore has content validity."

Based on this guidance, the Sponsor used OHSA Item 1 as the primary endpoint for its additional clinical study, Study 306, and generally presents the efficacy data throughout this Briefing Document as measured by OHSA Item 1 (dizziness/lightheadedness).

Figure 4-1 The OHQ Scale



OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

4.4.1.1 Clinical Meaningfulness of OHSA Item 1

4.4.1.1.1 Minimally Important Difference

The OHSA Item 1 was validated along with the broader OHQ scale. Patient and expert interviews, along with literature reviews, clearly established that OHSA Item 1 was a valid concept and was well understood by patients. Notably, 95% of patients proactively described that dizziness, lightheadedness, feeling faint, or feeling like they might black out was a core symptom of their disease.

As specified in the FDA Guidance on Patient Reported Outcome (PRO) measures, the Minimally Important Difference (MID) for OHSA Item 1 was calculated using several methods. The clinical meaningfulness of a change for an individual patient should be interpreted using the range of these MID methods. Chelsea concludes that a change from Baseline of between 1.1 and 2.5 units is clinically meaningful to a patient (Table 4-2).

Table 4-2 MID Estimates for OHSA Item 1

	Study 301		Study 306	
MID Method	**n**	**Units**	**n**	**Units**
Anchor-based				
Anchor to Patient-rated CGI-I	48	-2.48	67	-2.21
Anchor to MDS-UDPRS 4 to 3 Change	-	-	60	-2.18
Distribution-based				
½ Standard Deviation Method	168	1.12	222	1.09
SEM Method	22	1.18	38	1.59

CGI-I=Clinical Global Impressions-Improvement; MID=minimally important difference; MDS-UDPRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale; OHSA=Orthostatic Hypotension Symptom Assessment; SEM=Standard Error Measurement.

Importantly, the MID is often misunderstood to represent the point difference that must be present between treatment groups in order for that difference to be considered clinically meaningful. However, it is important to understand the MID is a within-group phenomenon (Marquis et al, 2004) and that, in fact, it has been reported that the between-group effect size should be smaller than the MID (De La et al, 2004).

When interpreting MID results, the FDA recommends that the range across methods should be used to help define an *a priori* responder criterion. Ultimately whether any response criterion is clinically meaningful represents a judgment, but that problem is present with almost all endpoints except for survival. The MID range should be used in combination with responder analyses as presented in Sections 6.1.1.2.1 and 6.1.2.3.1 of this Briefing Document in order to determine the relative proportion of patients who gain a clinically meaningful benefit while on droxidopa treatment compared with placebo.

MID Methodology

A comparison of patient ratings from the primary PRO to other endpoints, which are easier to interpret, can provide an anchor with which to evaluate changes. These anchor-based calculations are further supported by distribution-based methods which also help define a meaningful change. Distribution-based methods are derived from population standard deviations and intra-cohort comparisons of test-retest reliability.

The OHSA Item 1 was compared with two different scales to anchor the observed changes.

The patient-rated Clinical Global Impression-Improvement (CGI-I) was a simple PRO scale where patients were asked to rate the total improvement in the severity of their OH regardless of whether or not they believed it was due entirely to drug treatment. The scale could be scored as 0-not assessed; 1-very much improved; 2-much improved; 3-slightly improved; 4-no change; 5-slightly worse; 6-much worse; 7-very much worse. The change in OHSA Item 1 is anchored to those patients who rated their disease as 'slightly improved.'

The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UDPRS) was administered only in Study 306. Within this scale, there is a question (Item 1.12) which queries "Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or laying down?" with responses of:

0: Normal: No dizzy or foggy feelings.
1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things.
2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down.
3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling.
4: Severe: Dizzy or foggy feelings cause me to fall or faint.

The mean change in OHSA Item 1 was anchored to patients who rated their disease improving 1 unit on the MDS-UPDRS Item 1.12.

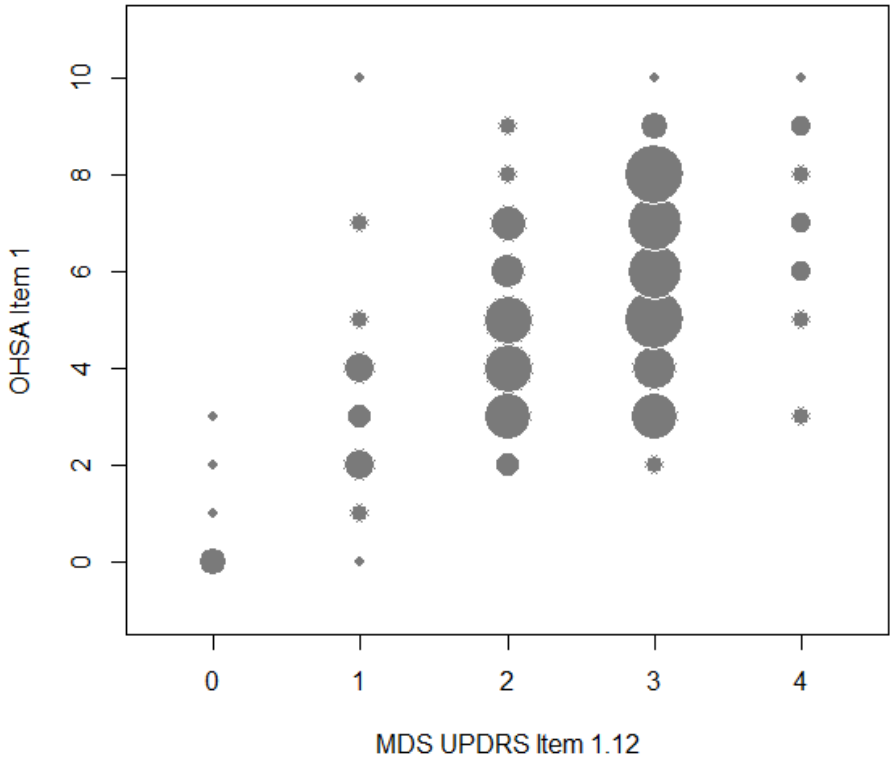
4.4.1.1.2 Functional Impairment as Related to OHSA Item 1

There is little information on how BP or symptoms correlate to functional outcomes in patients with nOH. However, in Study 306, patients were also administered the MDS-UPDRS which contains an item (Item 1.12, as described above) that requests patients estimate how they functionally respond to their symptoms of nOH.

Figure 4-2 below shows a correlation between OHSA Item 1 patient scores compared with their response on the MDS-UPDRS Item 1.12. The size of the bubble indicates the number of patients in each group. While there are a variety of responses to OHSA Item 1 as compared with the MDS-UPDRS Item 1.12, it is clear the two measures are correlated. Furthermore, it appears that patients with an absolute OHSA Item 1 score at Baseline of <3 are unlikely to have significant functional impairment. Alternatively, scores from 3 to 5 are well correlated to patients with

function impairments, including "needing to hold onto something," or to be "forced to sit or lay down." Scores over 5 are well correlated to major functional impairment, including being "forced to sit or lay down," or having actual syncopal episodes.

Figure 4-2 Correlation Between OHSA Item 1 and MDS-UPDRS Item 1.12



OHSA=Orthostatic Hypotension Symptom Assessment; MDS-UPDRS=Movement Disorder Society-Parkinson's Disease Rating Scale.
Note: The size of the bubbles corresponds with the number of patients with the observed values.

4.4.2 Blood Pressure

Blood pressure is an important physiological endpoint in the study of nOH; however, it is not a validated surrogate endpoint for clinical benefit. The fall in BP upon standing and the subsequent cerebral hypoperfusion is central to the symptomology of nOH and likely contributes to the increased morbidity and mortality in nOH patients (see Section 1.2.2). However, due to autonomic dysfunction, BP is a highly variable measure in nOH patients. Use of BP as a clinical endpoint is further complicated by the difficulty of measuring cerebral perfusion, and the lower correlation of brachial BP measurement to the underlying pathophysiology of the disorder. Therefore, single brachial BP measurements are useful endpoints in an nOH trial, but may not correlate well to actual symptomatic benefit. Studies using more rigorous BP measurement, such as continuous in-patient monitoring or ambulatory BP monitoring, are likely more informative when studying nOH treatments.

Due to the uncertain relationship between changes in standing BP and symptomatic benefit, the FDA has required that nOH treatments show improvements on symptomatic clinical endpoints to receive approval. The Chelsea-sponsored Phase 3 trials only include BP as a single brachial measurement to provide supplemental information to the symptomatic endpoints within the studies.

During the Chelsea-sponsored studies, BP was measured at each visit using the Orthostatic Standing Test (OST). The OST consisted of supine (head and torso elevated at approximately 30° from horizontal) SBP and DBP measurements at 10 minutes, 5 minutes, and immediately prior to standing, and 3 minutes post-standing; a final measurement was taken after patients were seated for 5 minutes after the standing test was complete (i.e., at 8 minutes after standing was initiated).

The OST was conducted 3 hours after the first daily dose of study medication to coincide with predicted peak BP effects. Blood pressure was allowed to be taken either by aneroid or mercury column sphygmomanometry or with valid digital devices, and once a method was selected, it was to be used consistently. Chelsea provided digital BP machines to sites upon request.

Patients were not to be provided with BP measurement results taken during the studies to avoid biasing the completion of PROs.

4.4.3 Patient Falls

As previously discussed, more patients reported treatment-emergent adverse events (TEAEs) of fall in the placebo group (n=9) compared with the droxidopa group (n=1) in Studies 301 and 302. This observation, given the short (1- to 2-week) duration of those studies, led to the decision to prospectively collect data on falls via electronic patient diaries in both Studies 306A and 306B as an efficacy measure. The definition of a "fall" in Study 306 was similar to others commonly used and accepted as standard in the field, which was "unexpectantly coming to rest on the ground, floor, or just a lower level than where you started" (Gibson et al, 1987).

4.4.4 Clinical Global Impressions

The Clinical Global Impression-Severity (CGI-S) and CGI-I are widely used scales that are generally recognized as reliable, accurate, and relevant. Versions were adapted for the measurement of symptom severity and symptom improvement in patients with nOH. These measures were assessed by both clinicians and patients in studies conducted by the Sponsor during the development of droxidopa. Detailed analyses of CGI data are provided in Appendix 9; Section 10.9.

The CGI-S is a 7-point scale ranging from a score of 1 (normal; no symptoms) to 7 (most ill with OH). A reduction in score over a period of time is considered an improvement in symptoms. The CGI-I is a 7-point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the Baseline evaluation. Clinician-reported symptomatic measures such as the CGI scale can be less variable as an Investigator applies the scale to multiple patients. However, both the clinician- and patient-reported CGI scales provide independent symptomatic endpoints that support the efficacy of droxidopa.

5. REGULATORY HISTORY

5.1 Key Regulatory Events

A brief chronology of key regulatory events is provided below.

- **17 January 2007**: Droxidopa was granted Orphan Drug designation by the Office of Orphan Products Development
- **15 February 2008**: Granted SPA for Study 301
- **07 August 2008**: Granted Fast-Track designation
- **16 March 2011**: The Study 306B protocol and the results from Study 306A (Interim Analysis Dataset) were submitted to the Agency.
- **28 September 2011**: Original submission of NDA
- **23 February 2012**: Cardiovascular and Renal Drugs Advisory Committee; 7 to 4 votes favoring approval of droxidopa for the treatment of symptomatic nOH: 1 abstention, 1 non-vote
- **28 March 2012**: DCRP issues Complete Response (CR) Letter citing inconsistency of data and disproportionate site effects in Study 301 as the basis for requiring a second study confirming safety and efficacy of droxidopa.
- **02 May 2012**: End-of-review Conference with DCRP to further discuss the CR Letter. DCRP requested additional information on Study 301, Site 507, and blinding of Study 306. The DCRP tentatively agreed to consider Study 306B as a second supportive study.
- **30 May 2012:** Sponsor submits additional information supporting the blinding of Study 306
- **29 June 2012**: DCRP issues General Advice Letter stating Study 306B is unlikely acceptable as a second positive study due to the theoretical potential for unblinding at the time of the interim analysis.
- **11 July 2012**: Sponsor informs clinical investigators that Study 306B is being stopped prematurely with a final enrollment date of 31 July 2012 because of the DCRP Advice Letter.
- **12 December 2012**: Sponsor submits a Formal Dispute Resolution Request to the Director, Office of New Drugs (OND) seeking a review of the DCRP CR Letter and proposing accelerated approval of droxidopa based on the original NDA.
- **10 January 2013**: Formal Dispute Resolution Meeting between the Sponsor and the Director of the OND

- **8 February 2013:** Director of the OND issues a Formal Dispute Resolution Response which upholds the DCRP CR Letter, denying immediate accelerated approval of droxidopa. The Response also a) indicates that Study 306B has the potential to serve as a second positive study, and b) that short-term endpoints are acceptable for approval of droxidopa, with the potential to confirm long-term efficacy post-marketing.

- **20 March 2013:** Type A Meeting between the Sponsor and DCRP held to discuss the format and content of the NDA resubmission. In this meeting, DCRP raised the potential for accelerated approval for droxidopa, using short-term clinical endpoints as surrogates for long-term benefit.

- **29 April 2013**: Sponsor submits a draft protocol for a post-marketing study (nOH401) to potentially confirm durability of effect. A second post-marketing study for the same purpose is planned and the synopsis of the study was included in the NDA resubmission.

- **14 August 2013**: Agency accepts Sponsor NDA resubmission

5.2 Regulatory Communications

5.2.1 Agency Conclusions Following Review of NDA

Inconsistency of Overall Findings

Following the submission and review of NDA 203202, the Sponsor received a CR Letter from DCRP. Included in the CR Letter was DCRP's rationale for not approving droxidopa on the basis of the submitted data. This rationale centered on "inconsistencies in the overall findings" including the "disproportionate contribution of Site 507 to the overall results of Study 301," as is summarized below:

> ***Complete Response Letter (28 March 2012)***: "Inconsistencies in the overall findings, therefore, constitute a reasonable basis for not accepting study 301 alone as adequate evidence of effectiveness," and "The disproportionate contribution of site 507 to the overall results of study 301 diminishes the persuasiveness of the study, providing an even stronger reason for not accepting study 301, the sole positive study, as adequate evidence of effectiveness."

Durability of Effect

The Division also stated in the CR Letter that it was "important to provide evidence of durability of droxidopa's treatment effect" and that this "has not been addressed adequately in your development program." The Division suggested that the Sponsor conduct an additional "study designed to demonstrate durability of effect over a 2- to 3-month period."

In his response to the Formal Dispute Resolution Request, however, the Director of OND stated his opinion that "data strongly demonstrating short-term clinical benefits…would be adequate for approval, with a possible requirement to verify durable clinical benefit postapproval."

Potential Pathways to Approval

In meetings that occurred subsequent to the Response to the Formal Dispute Resolution Request, the Division stated that both full approval and accelerated approval could be considered for droxidopa:

> **Minutes from Meeting with DCRP (10 March 2013):** "Depending on the data submitted in the NDA, the Agency could consider full approval for treatment up to 1 week, as well as accelerated approval with a 1-week treatment effect serving as a surrogate for a longer-term effect."

Sponsor Response to Agency

Study 301 clearly demonstrates the safety and short-term efficacy of droxidopa, although it does not meet all criteria for approving agents based upon a single study as listed in the Agency's guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998). Therefore, the Sponsor is submitting Study 306B, a second adequate and well-controlled study prospectively demonstrating that droxidopa improves the signs and symptoms of patients with nOH and provides independent substantiation of conclusions drawn from Study 301.

To further characterize the effect of droxidopa, the Sponsor has initiated a 450 patient randomized, placebo-controlled trial (intended as a post-marketing study) with a 3-month treatment period. Topline data from this study are expected in late 2016.

6. OVERVIEW OF EFFICACY

6.1 Short-Term Pivotal Efficacy Studies

Two randomized, placebo-controlled, double-blind, induction-design studies (Studies 301 and 306B) and one placebo-controlled randomized-withdrawal study (Study 302) establish the short-term safety and efficacy of droxidopa.

6.1.1 Study 301

Study 301, reviewed and conducted under an SPA (Section 5.1), was a pivotal Phase 3, multi-center, multi-national, double-blind, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose-titration period prior to a 7-day washout period, followed by a 7-day randomized treatment period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo. Study 301 was conducted in patients with symptomatic nOH associated with PD, MSA, PAF, DβH Deficiency, or NDAN. Key inclusion and exclusion criteria are presented in Table 6-1; these criteria were similar across all short-term pivotal studies.

Table 6-1 Study 301: Key Inclusion and Exclusion Criteria

Key Inclusion Criteria
Clinical diagnosis of OH associated with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, or NDAN
Documented fall in standing SBP ≥ 20 mmHg or DBP ≥ 10 mmHg
Key Exclusion Criteria
Taking vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine (within 2 days of study entry)
Taking anti-hypertensive medication (use of short-acting, anti-hypertensive medications at bedtime were permitted). All other medications were to be kept stable while on the study.
Pre-existing severe supine hypertension: BP ≥ 180/110 mmHg
Significant systemic, hepatic, cardiac, or renal illness
Diabetes mellitus or insipidus
Mental disorder that interfered with the diagnosis and/or conduct of study

The pre-specified primary efficacy endpoint was the mean change in the OHQ composite score from Randomization to End of Study. Based on an overall 0.05 two-sided significance level, the study had greater than 80% power to detect a difference of 1.2 units in the OHQ composite score (primary variable) with 75 evaluable patients in each randomized treatment group in a 1:1 ratio (i.e., 150 patients in total). The study was originally designed with OHSA Item 1 (dizziness/lightheadedness) as the primary endpoint. However, based on results from Study 302 (which completed prior to Study 301) showing efficacy on the full OHQ composite score endpoint, and after discussions with the Agency, the primary endpoint in Study 301 was changed to the OHQ composite score prior to the study being unblinded. The Agency agreed the SPA remained in place after this endpoint change.

The study design is presented graphically in Figure 6-1 (see Appendix 2; Table 10-1 for a tabular summary of study results). As part of the study design, all patients entered an open-label, dose titration/optimization period, where they were titrated to effect. Dose titration began at 100 mg TID of droxidopa and was escalated in 100 mg TID increments until one or more of the following criteria were met (stopping rules):

1. The patient became both asymptomatic (i.e., a score of "0" on Item 1 of the OHSA) and had an improvement in standing SBP of at least 10 mmHg relative to Baseline (all measurements made 3 minutes post-standing);
2. The patient had a sustained SBP of greater than 180 mmHg or DBP of greater than 110 mmHg after 3 minutes of standing or after 5 minutes of sitting (i.e., 8 minutes post-standing), OR a sustained SBP greater than 180 mmHg or DBP greater than 110 mmHg measured in the supine (head and torso elevated at approximately 30° from horizontal) position;
3. The patient was unable to tolerate side effects believed to be related to the study drug; and
4. The patient reached the maximum dose of 600 mg TID (1800 mg/day) droxidopa.

During the titration period, a composite parameter was used to determine if patients were Responders to droxidopa therapy, which identified a response to treatment as:

- A change in symptoms of nOH, as indicated by an improvement of at least 1 unit on Item 1 of the OHSA (dizziness); and
- An improvement in SBP of at least 10 mmHg at 3 minutes post-standing.

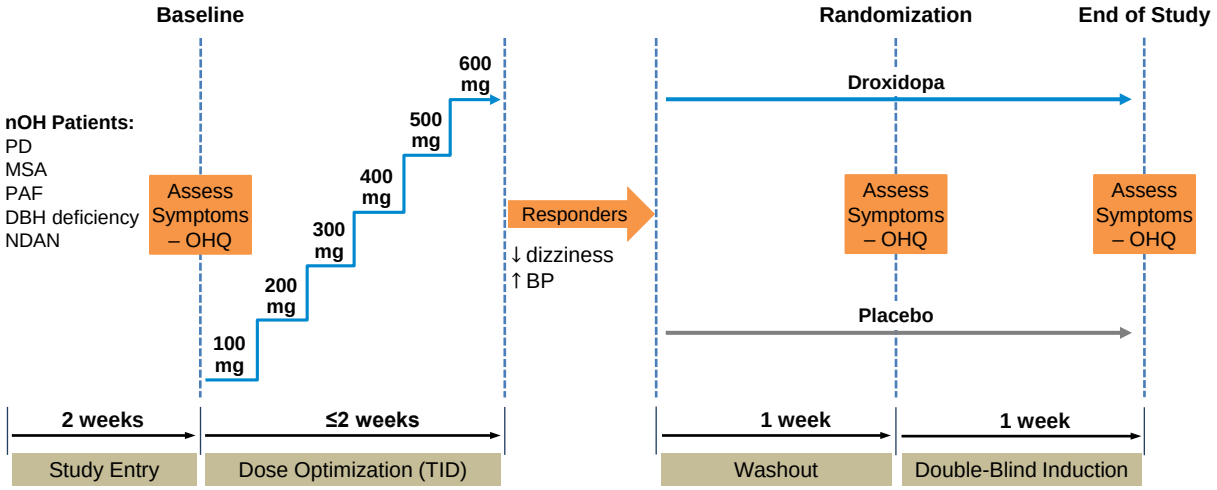
Patients who were defined as being Responders to open-label droxidopa treatment (by both BP and symptomatic improvement) were entered into the washout period and subsequently randomized into the double-blind treatment period at the highest tolerated dose at which they qualified as a Responder.

Patients who met any of the following dose escalation discontinuation criteria were considered treatment failures and were not entered into the double-blind treatment period of the study:

- Patients who met criterion 2 or 3 and did not qualify as a Responder at the previous lower dose;
- Patients who met criterion 2 or 3 at the initial dose of 100 mg TID; or
- Patients who met criterion 4 and did not qualify as a Responder at any dose.

The same open-label, dose titration/optimization period was conducted in Study 302.

Figure 6-1 Study 301: Study Design



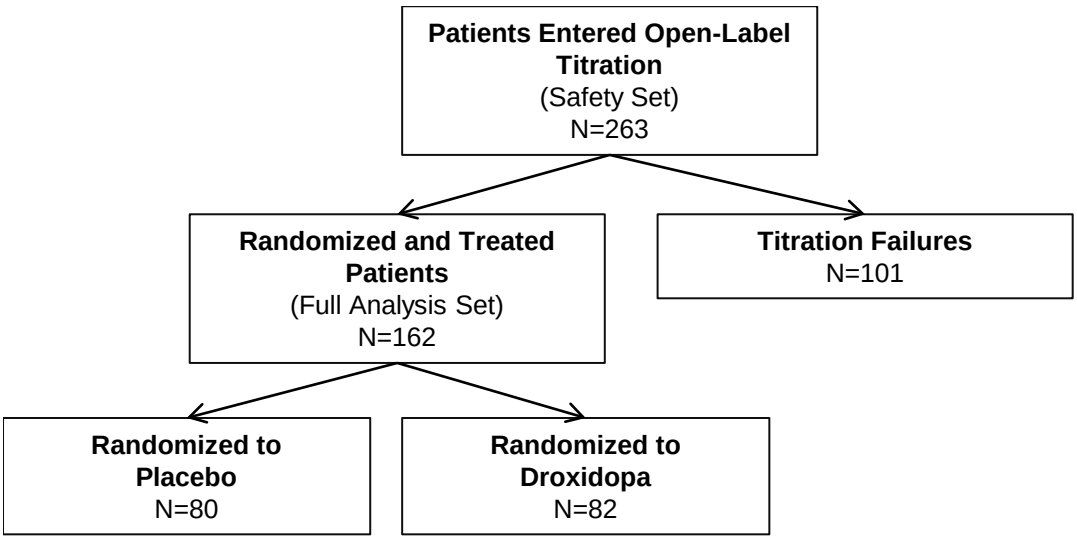
DBH=dopamine beta hydroxylase; MSA=Multiple System Atrophy; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; OHQ=Orthostatic Hypotension Questionnaire; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; TID=three times daily.

6.1.1.1 Disposition, Demographics, and Concomitant Medications

6.1.1.1.1 Disposition

Out of the reported 354 patients screened in Study 301, 263 eligible patients entered the open-label dose-titration period (Figure 6-2). Of those, 168 patients successfully completed the open-label titration period and were considered responders and were subsequently randomized into the double-blind treatment period. Of the 168 patients randomized, 6 patients did not receive blinded study drug and were excluded from the Full Analysis Set (FAS; a modified Intent-to-Treat [mITT] analysis set that included patients who were randomized and received at least 1 dose of double-blind study drug). Therefore, the FAS consisted of 162 patients: 80 patients randomized to placebo and 82 patients randomized to droxidopa. Of the 162 patients in the FAS, 77 of 80 patients randomized to placebo and all 82 patients randomized to droxidopa completed (at least 7 days of treatment) the study.

Figure 6-2 Study 301: Patient Disposition



Based on a *post-hoc* evaluation, of the 101 patients treated with droxidopa only during the open-label titration phase (i.e., patients who were classified as titration failures and did not receive double-blind study drug), the most common reason for discontinuation was reaching the maximum dose without meeting the response criteria (40 [39.6%] patients), followed by AEs (19 [18.8%] patients), a Sponsor enrollment cap (19 [17.8%] patients), BP elevation (8 [7.9%] patients), and withdrawn consent (6 [5.9%] patients). The majority of patients (85%) excluded from the study for failure to meet response criteria exhibited a symptomatic improvement but not the required 10 mmHg increase in standing SBP.

6.1.1.1.2 Demographics

Demographic characteristics were similar between the droxidopa and placebo treatment groups (Table 6-2).

Table 6-2 Study 301: Summary of Demographic and Baseline Characteristics (Safety Set)

	RCT Phase	
	Placebo (N=81)	**Droxidopa (N=81)**
Sex [n (%)]		
Male	43 (53.1)	41 (50.6)
Female	38 (46.9)	40 (49.4)
Race [n (%)]		
White	76 (93.8)	81 (100.0)
Black/African American	1 (1.2)	0
Asian	1 (1.2)	0
Hispanic/Latino	3 (3.7)	0
Primary Clinical Diagnosis [n (%)]		
Parkinson's Disease	31 (38.3)	35 (43.2)
Multiple System Atrophy	12 (14.8)	14 (17.3)
Pure Autonomic Failure	28 (34.6)	26 (32.1)
Dopamine Beta Hydroxylase Deficiency	0	0
Non-Diabetic Autonomic Neuropathy	6 (7.4)	2 (2.5)
Other Diagnosis	4 (4.9)	4 (4.9)
Age (Years) at Screening		
Mean (SD)	55.8 (19.94)	57.3 (16.98)
Min, Max	18, 87	20, 84
Geographic Region [n (%)]		
US	33 (40.7)	32 (39.5)
Non-US	48 (59.3)	49 (60.5)
Disease Severity		
Mean Baseline Dizziness, n	79	81
Mean (range)	6.2 (1,10)	6.5 (3,10)
Baseline SBP upon Standing +3 Minutes (mmHg), n	80	82
Mean (SD)	90.7 (16.83)	90.8 (15.63)

Max=maximum; Min=minimum; RCT=Randomized-Controlled Treatment; SBP=systolic blood pressure; SD=standard deviation; US=United States.

Note: Demographic data are based on the Safety Set. Disease severity (the mean Baseline Orthostatic Hypotension Symptom Assessment [OHSA] Item 1 Score) and Baseline SBP upon standing data are based on the Full Analysis Set with missing data excluded.

6.1.1.1.3 Concomitant Medication

Overall, concomitant medication use was typical of the patient population and was similar between the droxidopa and placebo groups. Patients were instructed not to change their concomitant medication use during the study.

The majority of patients in the study took concomitant medications. In the Randomized-Controlled Treatment (RCT) phase, 61 (75.3%) placebo-treated and 63 (77.8%)

droxidopa-treated patients took concomitant medications. DOPA and DOPA derivatives were the most common concomitant medications by Anatomical Therapeutic Chemical (ATC) class and their use was comparable between placebo-treated (39.5%) and droxidopa-treated patients (39.5%). Sinemet (carbidopa/levodopa) was the most commonly used DOPA derivative, taken by 29.6% of placebo-treated and 25.9% of droxidopa-treated patients. Mineralocorticoids (fludrocortisone) were taken by 22.2% of placebo-treated and 25.9% of droxidopa-treated patients.

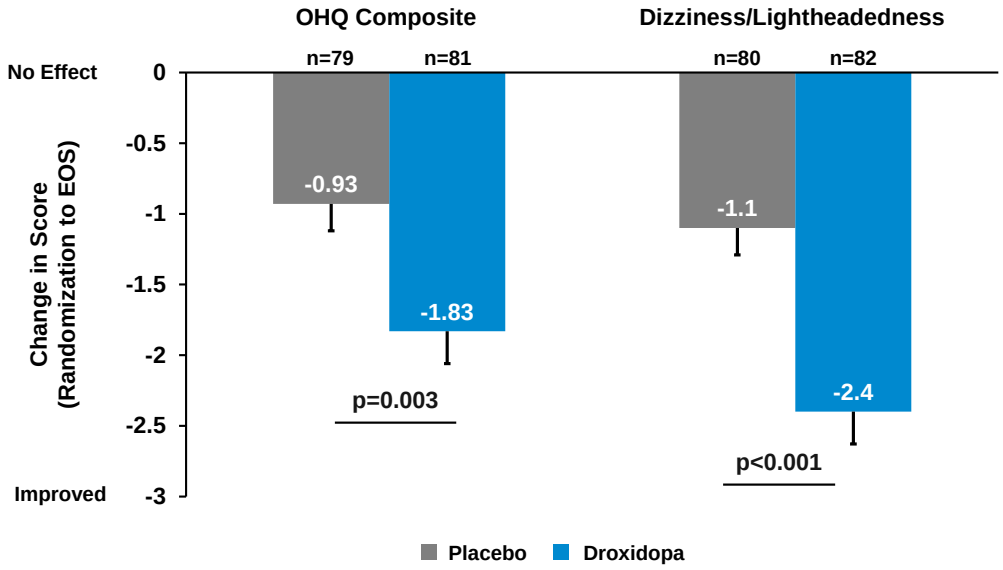
Overall, concomitant medication use was typical of the patient population. There were no clinically meaningful differences in concomitant medication use by ATC class or drug name observed between placebo-treated and droxidopa-treated patients in the RCT phase.

6.1.1.2 OHQ Composite Score and Dizziness (OHSA Item 1)

In Study 301, the mean change in the OHQ composite score from Randomization to End of Study (i.e., Week 1) showed statistically significant benefits favoring droxidopa (p=0.003; Figure 6-3 and Table 6-3). At End of Study, droxidopa-treated patients had a mean decrease of 1.83 units in their OHQ composite score (indicating improvement in symptom severity and daily activity) compared with a 0.93 unit decrease in the placebo patients, resulting in a difference between placebo and droxidopa of 0.90 units favoring droxidopa.

The mean change from Randomization to End of Study in dizziness/lightheadedness (OHSA Item 1, the cardinal symptom of nOH) was the original primary efficacy endpoint for Study 301 and continued to be a pre-specified secondary endpoint (see Section 6.1.1). At End of Study, droxidopa-treated patients had a mean decrease from Randomization of 2.4 units in their OHSA Item 1 score compared with a 1.1 unit decrease in placebo-treated patients, resulting in an overall statistically significant treatment difference of 1.3 units favoring droxidopa (p<0.001; Figure 6-3 and Table 6-3).

Figure 6-3 Study 301: OHQ Composite Score and Dizziness (OHSA Item 1) (FAS, LOCF)



ANCOVA=analysis of covariance; EOS=End of Study; FAS=Full Analysis Set; LOCF=last observation carried forward; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: For analysis of OHQ Composite Score: the p-value from ANCOVA model included a factor for randomized treatment along with the OHQ composite value at Randomization as a covariate. For analysis of OHSA Item 1: the p-value from non-parametric ANCOVA. ANCOVA was adjusted for the covariate respective OHSA Item score at Randomization.

In Study 301, the hierarchy of endpoints was prospectively defined in the statistical analysis plan (SAP). The data presented in Table 6-3 represent mean changes from Randomization to End of Study. In addition to showing benefits on the primary endpoint for Study 301 (OHQ composite score), the first 5 pre-specified secondary endpoints were all statistically significantly in favor of droxidopa.

Table 6-3 Study 301: Results from the Pre-specified Hierarchy of Efficacy Endpoints (FAS, LOCF)

	Placebo (N=80)		Droxidopa (N=82)			
Efficacy Endpoints	**n**	**Δ Mean (SD)**	**n**	**Δ Mean (SD)**	**Treatment Difference**	**p-value**
Primary Efficacy Endpoint						
OHQ Composite Score	79	-0.93 (1.69)	81	-1.83 (2.07)	-0.9	0.003[1]
Secondary Efficacy Endpoints						
OHDAS Composite Score	79	-0.92 (1.82)	81	-1.98 (2.31)	-1.06	0.003[1]
OHSA Composite Score	79	-0.95 (1.90)	81	-1.68 (2.13)	-0.73	0.010[1]
OHDAS Item 1 (standing short time)	80	-0.8 (2.60)	82	-1.9 (2.75)	-1.1	0.003[2]
OHDAS Item 3 (walking short time)	80	-0.6 (2.37)	82	-1.7 (2.55)	-1.1	0.009[2]
OHSA Item 1 (dizziness/lightheadedness)	80	-1.1 (2.58)	82	-2.4 (3.20)	-1.3	<0.001[2]

ANCOVA=analysis of covariance; Δ=change; FAS=Full Analysis Set; LOCF=last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SD=standard deviation.

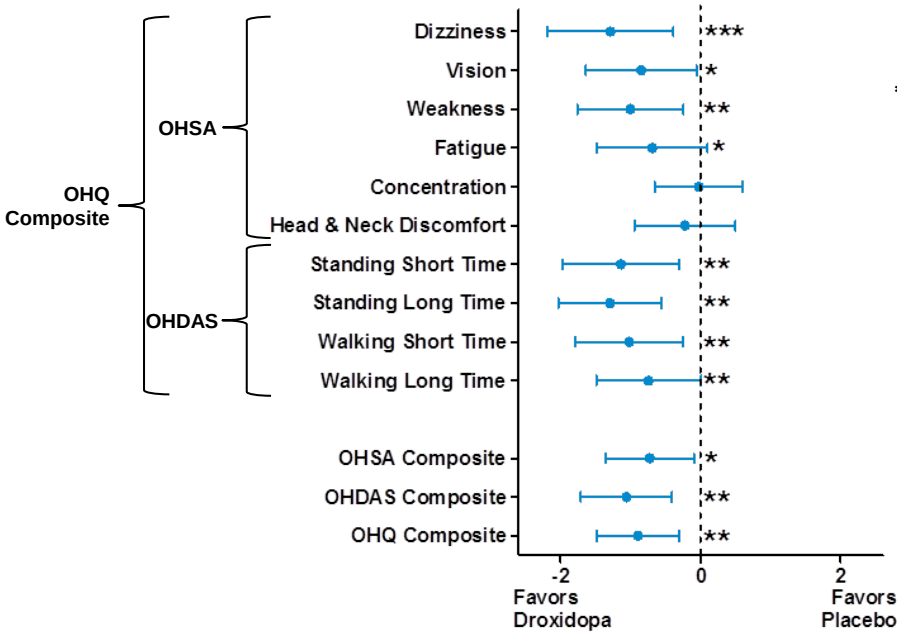
Note: Efficacy endpoints are presented in hierarchical order.

1 The p-value from ANCOVA model included a factor for randomized treatment along with the score at Randomization as a covariate.

2 The p-value from non-parametric ANCOVA using Cochran-Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate respective item score at Randomization.

In addition to the benefits observed based on results from the OHQ composite score and OHSA Item 1 (dizziness/lightheadedness), droxidopa-treated patients experienced benefits across a broad range of other symptoms as well as the impact of these symptoms on their ability to perform activities of daily living (Figure 6-4). Eight of 10 individual items of the OHQ measuring symptomatic benefit or the impact of symptoms on daily activities (as well as all 3 composite scores) showed statistically significant benefits in favor of droxidopa. The consistent improvements observed across the multiple individual items and composite scores within the OHQ demonstrate the breadth of benefit associated with droxidopa.

Figure 6-4 Study 301: Treatment Differences for OHQ Components (FAS, LOCF)



ANCOVA=analysis of covariance; FAS=Full Analysis Set; LOCF=last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using either a parametric or a non-parametric (as specified in the Statistical Analysis Plan) ANCOVA model including a factor for randomized treatment along with the value at Randomization as a covariate (*p<0.05; **p<0.01; ***p<0.001). Confidence intervals are not adjusted for covariates and may cross the zero line despite statistical significance.

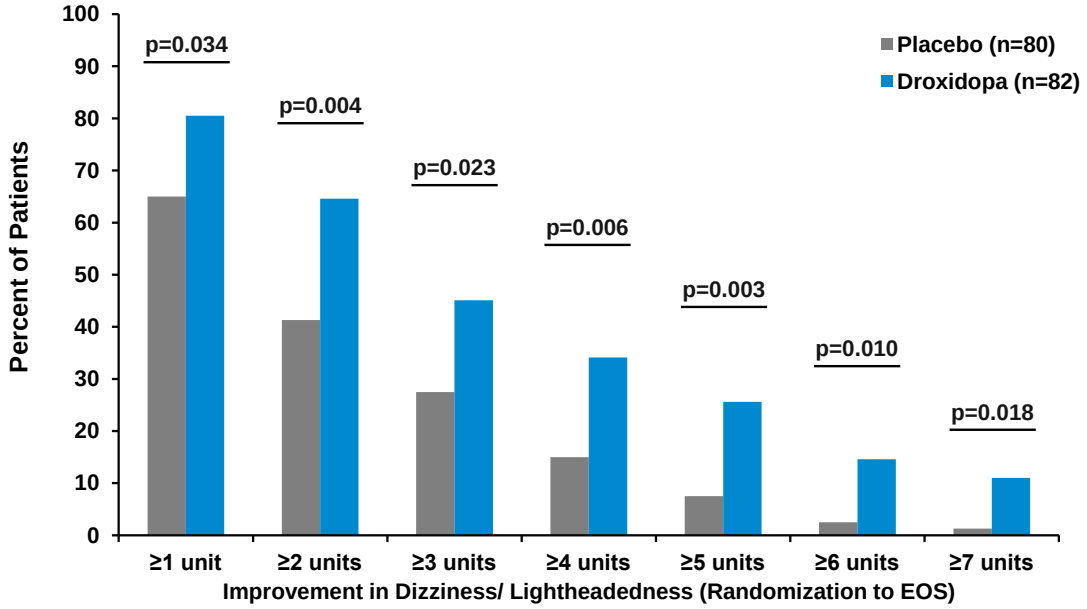
6.1.1.2.1 Evidence of Efficacy from Multiple Supportive Analyses

In addition to the important clinical data from Study 301 demonstrating the significant benefits of droxidopa on the mean change from Randomization to End of Study on OHSA Item 1 (dizziness/lightheadedness), there exist data from multiple other *post-hoc* analyses that independently corroborate and substantiate important conclusions drawn from the results of the mean change from Randomization to End of Study analysis. These are summarized below.

Responder Analyses of OHSA Item 1

Based on results from the *post-hoc* analysis, Study 301 demonstrated larger treatment differences in favor of droxidopa based on unit improvements from Randomization to End of Study in the OHSA Item 1 score regardless of the unit change of the response ($p \leq 0.034$; Figure 6-5).

Figure 6-5 Study 301: Dizziness (OHSA Item 1) Responders Analysis (FAS, LOCF)

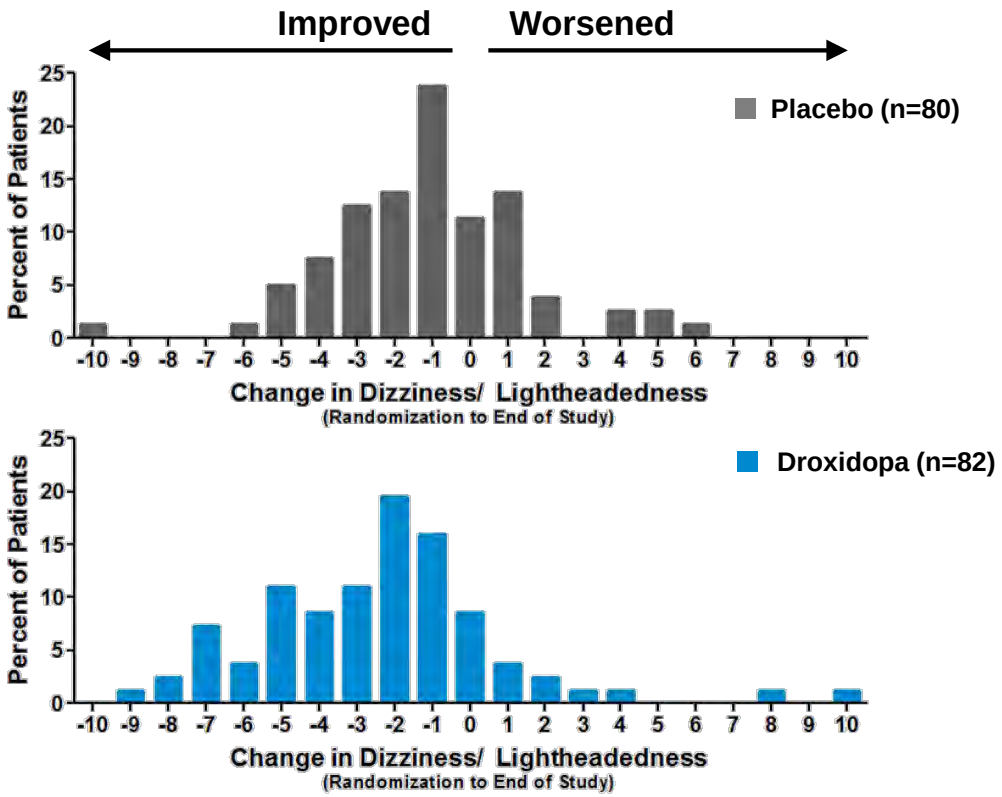


EOS=End of Study; FAS=Full Analysis Set; LOCF=last observation carried forward; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Treatment differences tested using Fisher's Exact Test.

Bin Analyses of OHSA Item 1

In Study 301, when patients are grouped according to their actual dizziness response and each patient is only included once, more droxidopa-treated patients experienced improvements and fewer droxidopa-treated patients worsened compared with placebo-treated patients from Randomization to End of Study in the OHSA Item 1 score (Figure 6-6).

Figure 6-6 Study 301: Distribution of Changes in the Dizziness (OHSA Item 1) Score (FAS, LOCF)



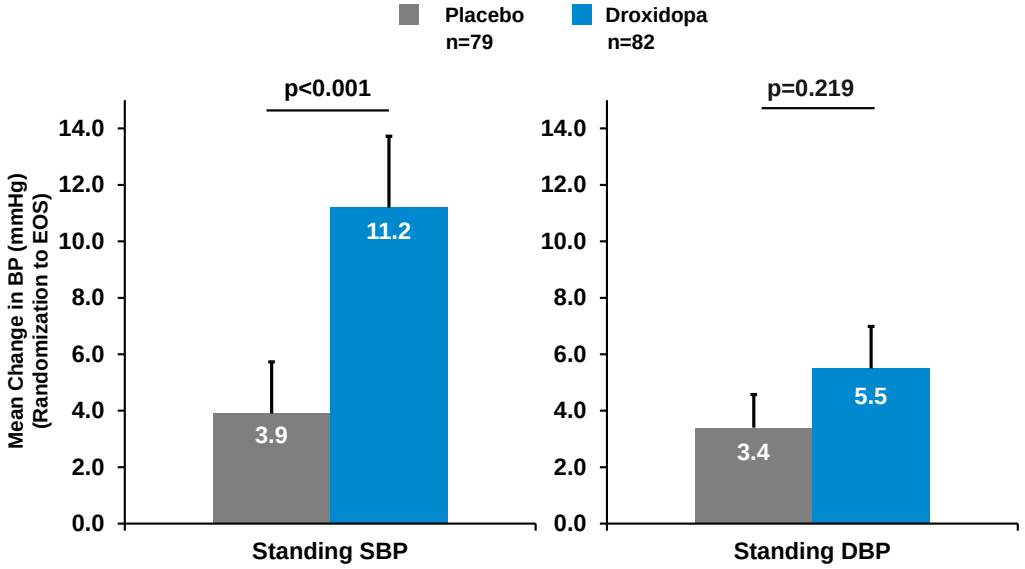
FAS=Full Analysis Set; LOCF=last observation carried forward; OHSA=Orthostatic Hypotension Symptom Assessment.

6.1.1.3 Standing Blood Pressure Response at Week 1

Blood pressure is an important pharmacodynamic measure which has a weak correlation to symptomatic improvements in nOH patients.

Although Study 301 was not specifically designed to demonstrate significant increases in BP, the change in standing BP was a pre-specified secondary efficacy endpoint of the study. Patients receiving droxidopa experienced a statistically significant change from Randomization to End of Study in standing SBP compared with placebo: mean change in standing SBP of 11.2 mmHg following treatment with droxidopa compared with 3.9 mmHg following treatment with placebo ($p<0.001$), resulting in a difference between placebo and droxidopa of 7.3 mmHg favoring droxidopa (Figure 6-7). Treatment with droxidopa also resulted in numerically superior improvements in standing DBP from Randomization to End of Study compared with placebo.

Figure 6-7 Study 301: Increase in Standing Blood Pressure (FAS, MDE)



ANCOVA=analysis of covariance; DBP=diastolic blood pressure; FAS=Full Analysis Set; MDE=missing data excluded; SBP=systolic blood pressure.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for the Baseline or Randomization value as a covariate (SBP) or a parametric ANCOVA with treatment and value at randomization as factors (DBP).

6.1.1.4 Clinical Global Impressions of Severity and Improvement

In Study 301, there was an improvement in symptom severity (CGI-S) during the study for both the clinician- and patient-rated assessments in both the droxidopa and placebo groups (Appendix 9; Table 10-11). While there was no statistical difference observed between droxidopa and placebo groups, a greater percentage of droxidopa-treated patients (43.9%) showed improvement by at least 1 point in clinician-rated assessments from Randomization to End of Study when compared with placebo-treated patients (33.8%); similar results were observed in patient-rated improvement (58.5% and 46.3%, respectively).

Improvements at End of Study (CGI-I) were also observed for both the clinician- and patient-rated assessments in both the droxidopa and placebo groups (Appendix 9; Table 10-12). While there was no statistical difference observed between droxidopa and placebo groups, a greater percentage of droxidopa-treated patients (75.6%) were clinician-rated as "Very much – Slightly Improved" compared with placebo-treated patients (63.8%); a similar result was observed in patient-rated improvement (75.3% and 65.0%, respectively).

6.1.1.5 Sensitivity Analyses

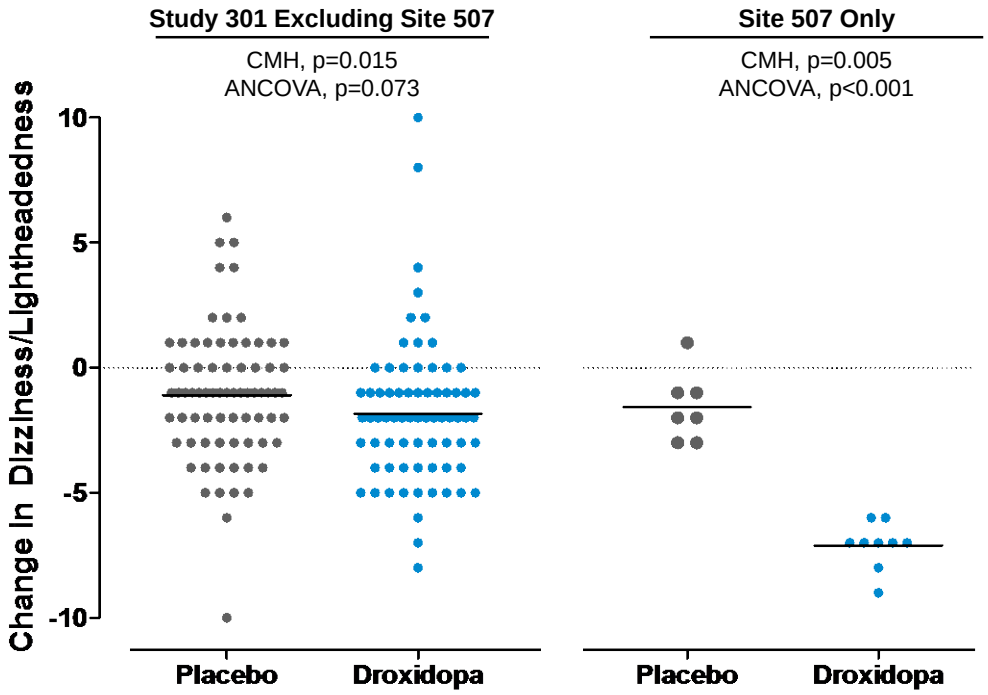
6.1.1.5.1 Site 507

As outlined in Section 5.2, the Agency stated in its CR Letter that "the disproportionate contribution of Site 507 to the overall results of Study 301 diminishes the persuasiveness of the

study." The Agency reiterated this position in the General Advice Letter (dated 29 June 2012). The Agency noted that when data from the largest site in Study 301, Site 507 (16 patients of the 162 total), located in the Ukraine, were removed from the overall Study 301 FAS (Figure 6-8 and Figure 6-13), Study 301 loses statistical significance based on the analysis of mean change from Randomization to End of Study in OHSA Item 1 based on an analysis of covariance (ANCOVA) analysis, although a trend (p=0.073; 0.7 unit treatment difference) remains; results from Site 507 alone were highly statistically significant.

It is important to note that the pre-specified primary analysis of Study 301 was based upon the Cochran–Mantel–Haenszel test, given the distribution of the data. When data from Study 301 excluding Site 507 are evaluated in this manner, the study retains statistical significance (p=0.015; Figure 6-8).

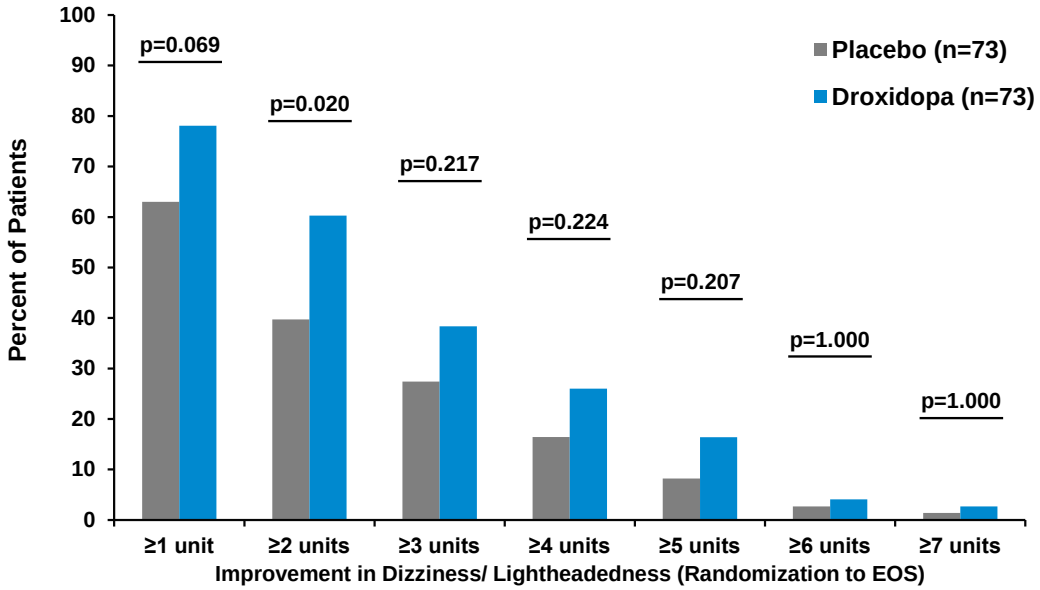
Figure 6-8 Per Patient Change in OHSA Item 1 from Randomization to End of Study; Site 507 Compared with Rest of Study



ANCOVA=analysis of covariance; CMH=Cochran–Mantel–Haenszel; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using both parametric ANCOVA and non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics, both adjusted for the Randomization value as a covariate.

With regard to the OHSA Item 1 unit improvement responder analysis, when Site 507 is removed from the analysis (Figure 6-9), the treatment difference between the droxidopa and placebo groups is lost for improvements ≥6 units. However, in all other unit-improvement categories <6 units, it is clear there remains a subset of patients who benefit from treatment with droxidopa across the range of responses.

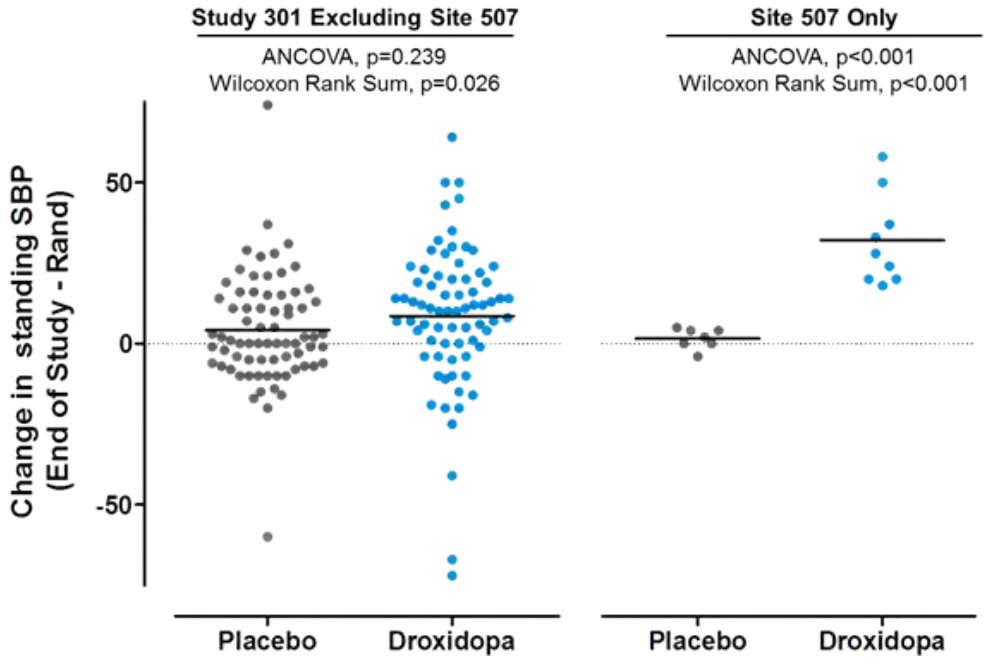
Figure 6-9 Site Effects in Study 301: Dizziness (OHSA Item 1) Responders (Data from Site 507 Excluded)



EOS=End of Study; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Treatment differences tested using Fisher's Exact Test.

In addition to the observation that statistical significance for OHSA Item 1 was lost when data from Site 507 were removed from the analysis, the Agency further noted that BP data at this site were highly homogenous, which raised questions from the Agency regarding study conduct and data integrity at the site. Similar to the OHSA Item 1 results, when standing SBP data from Site 507 were removed from the overall Study 301 FAS, the study loses statistical significance based on the mean change from Randomization for End of Study in standing SBP using an ANCOVA analysis; results from Study 507 alone were highly statistically (Figure 6-10).

Figure 6-10 Per Patient Change in Standing SBP (+3 min) from Randomization to End of Study; Site 507 Compared with Rest of Study



ANCOVA=analysis of covariance; min=minute; SBP=systolic blood pressure.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using parametric ANCOVA with treatment and the Randomization value as a covariate, and by the non-parametric Wilcoxon Rank Sum test.

An independent analysis evaluating Study 301 regarding the heterogeneity of data across clinical sites, including Site 507, with respect to efficacy outcomes is provided in Appendix 3 (Section 10.3).

6.1.1.5.1.1 Results from Monitoring Visits and Audits of Site 507

Due to the high enrollment at this site, frequent monitoring visits to Site 507 were performed during the conduct of the study and multiple audits were conducted during and after the study and during the review of the NDA, including a pre-approval inspection conducted by FDA (Table 6-4). In addition, enrollment was stopped in the Ukraine after a cap was reached. The Sponsor notes that an independent Directed Audit was conducted at Site 507 in which the auditor stated that he did not find sufficient reason to doubt the validity of the source data collected by this site for Study 301. Also, there was nothing discovered indicating that the blind was compromised or that study patients were not authentic.

During these visits/audits, no major data irregularities were identified by either Chelsea or the Agency. All source documents from the site were reviewed and submitted to the Agency. Examination of the source documents revealed that all the patients were both valid and met the study's inclusion criteria.

Table 6-4 Efforts to Ensure Data Validity: Study 301, Site 507

Auditor/Activity	*Date*	*Major Findings*
Routine Monitoring		
CRO	28 Apr 2009	None
CRO	18-19 May 2009	None
CRO	12 Jun 2009	None
CRO	23-24 Jun 2009	None
CRO	8-9 Jul 2009	None
CRO	17 Jul 2009	None
CRO	26 Aug 2009	None
CRO	30 Sep 2009	None
Independent Data Verification		
Second CRO	1-3 Feb 2011	None
Second CRO	11-13 Oct 2011	None
Second CRO	26 Dec 2011	None
Sponsor Visits and Audits		
Sponsor Site Visit	16 Jul 2009	None
CRO Quality Assurance Audit	25-26 Aug 2009	None
Directed Audit	5-8 Nov 2012	None
Provide Source Documents to FDA	8 Nov 2012	None
FDA Inspection Following Completion of Study 301		
FDA Pre-approval Inspection	20-25 Jan 2012	None

CRO=Contract Research Organization; FDA=Food and Drug Administration.

6.1.1.5.1.2 Demographics at Site 507

There were a number of differences in the demographic characteristics of patients enrolled at Site 507 compared with the overall study. While most of the patients in Study 301 had nOH from primary autonomic failure (MSA, PAF, PD), the majority of the patients at Site 507 had nOH secondary to autoimmune disorders (5 of the 16 patients), injuries (2 of the 16 patients), ischemic disease (2 of the 16 patients), and infection (1 of the 16 patients). These patients generally would be classified as having NDAN.

In addition to having an increased prevalence of secondary nOH compared with other study sites, patients at Site 507 tended to have more severe disease than the remainder of patients in Study 301 (Table 6-5), have lower mean standing SBP at Randomization, be younger, and were more likely to be male than female. In addition, in contrast to other patients in Study 301, patients at Site 507 generally did not have access to and all were naïve to any pharmacologic treatment, including fludrocortisone.

The atypical patient population at Site 507 may explain the outcomes at this site.

Table 6-5 Study 301: Site 507 Characteristics

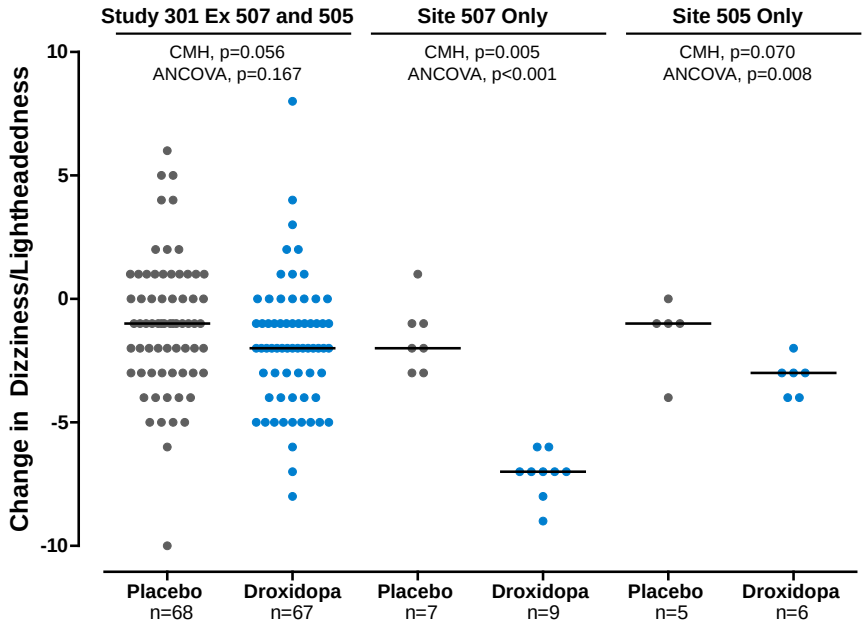
Patient Characteristics	Site 507 (N=16)	Study 301 Excluding Site 507 (N=146)
Dizziness/Lightheadedness (OHSA Item 1 score) at Randomization	8.3	5.1
Standing SBP at Randomization	93.3 mmHg	97.5 mmHg
Age at Screening	42.7 years	56.5 years
Male:Female ratio	1.67	1.03

OHSA=Orthostatic Hypotension Symptom Assessment; SBP=systolic blood pressure.

6.1.1.5.2 Site 505

After the CR Letter, the Agency identified a second Ukrainian site of potential concern. The Agency noted that OHSA Item 1 data from Site 505 alone was highly statistically significant and BP results were relatively homogeneous. Figure 6-11 (OHSA Item 1) and Figure 6-12 (BP) below show individual patient data for the overall study excluding Sites 505 and 507 and for Site 505 and Site 507 alone. Although the data at Site 505 were strongly positive favoring droxidopa, patients at Site 505 had a range of symptomatic responses with some overlap between treatment arms. Overall, Site 505 showed treatment effects consistent with data from other individual sites and Study 301 as a whole.

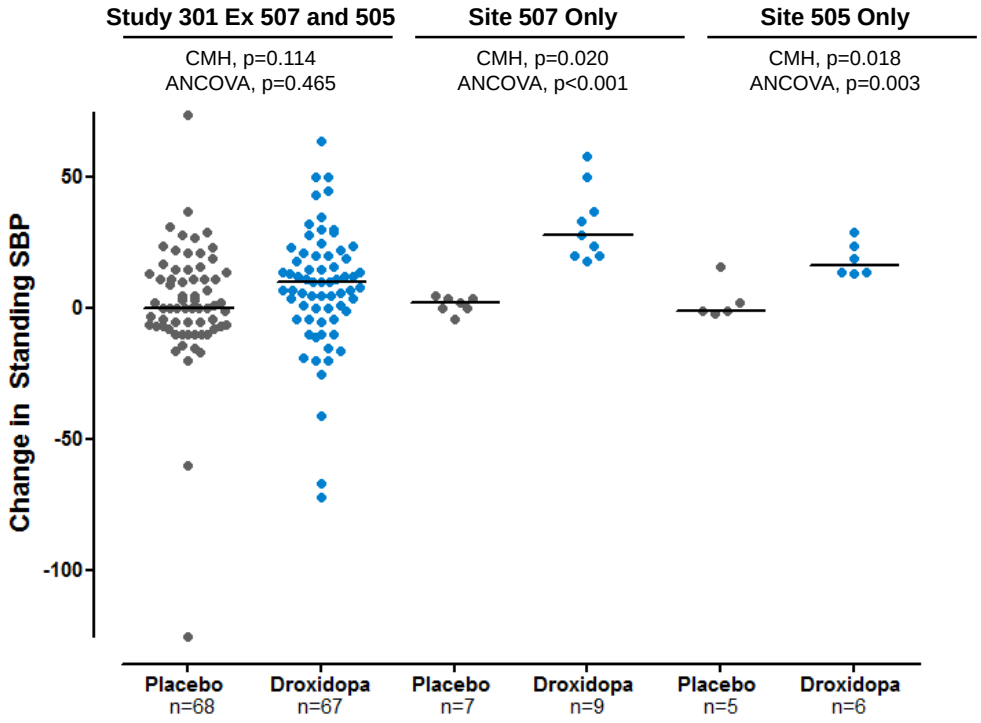
Figure 6-11 Per Patient Change in OHSA Item 1 from Randomization to End of Study; Sites 505 and 507 Alone Compared with Rest of Study



ANCOVA=analysis of covariance; CMH=Cochran–Mantel–Haenszel; Ex=excluding; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using both parametric ANCOVA and non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics, both adjusted for the Randomization value as a covariate.

Figure 6-12 Per Patient Change in Standing SBP (+3 min) from Randomization to End of Study; Site 505 and 507 Alone Compared with Rest of Study



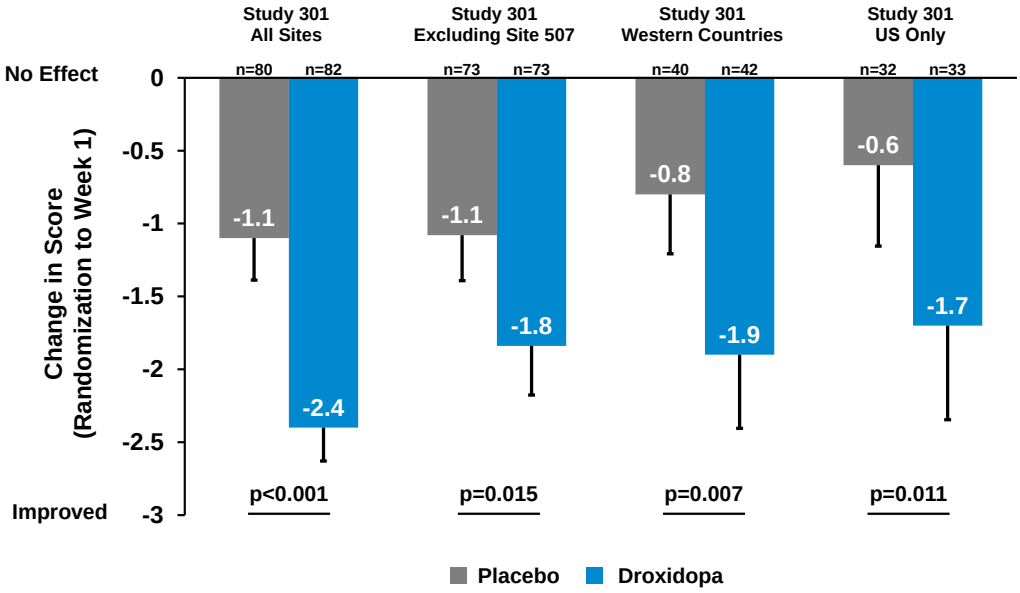
ANCOVA=analysis of covariance; CMH=Cochran–Mantel–Haenszel; Ex=excluding; SBP=systolic blood pressure.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using both parametric ANCOVA and non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics, both adjusted for the Randomization value as a covariate.

An independent analysis evaluating Study 301 regarding the heterogeneity of data across clinical sites, including Site 505, with respect to efficacy outcomes is provided in Appendix 3 (Section 10.3).

6.1.1.5.3 Regional Sensitivity Analyses

To assess the potential regional impact on the conclusions from Study 301, the Sponsor performed additional *post-hoc* sensitivity analyses by geographic region (Figure 6-13). When data from all Western countries, including the US, Canada, Australia, and Western Europe, are evaluated, there are treatment differences favoring droxidopa compared with placebo in the mean change from Randomization to End of Study in OHSA Item 1 (treatment difference over placebo of 0.9 units; p=0.007). Furthermore, when looking at data from US sites alone, a subgroup of 65 patients, there is also a treatment difference in favor of droxidopa in the mean change from Randomization to End of Study in OHSA Item 1 (treatment difference over placebo of 1.1 units; p=0.011).

Figure 6-13 Study 301 Regional Sensitivity Analyses: Change in OHSA Item 1 from Randomization to End of Study



ANCOVA=analysis of covariance; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to changes from Baseline and Randomization were evaluated using non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for the Baseline or Randomization value as a covariate.

Note: Western countries are United States, Canada, Austrialia, and Western Europe.

6.1.1.5.4 Conclusions on Site Effects in Study 301

Due to the limited number of patients in this indication, removal of large sites or subgroups is expected to have significant effects on the statistical significance of a study. In addition, caution should be maintained when drawing conclusions from *post-hoc* analyses of small subpopulations. Importantly, droxidopa maintains a treatment benefit over placebo even when removing multiple, large clinical sites from the Intent-to-Treat (ITT) population.

6.1.1.6 Efficacy Conclusions from Study 301

Study 301 conclusively demonstrates the efficacy of droxidopa by showing improvements on dizziness, numerous other symptomatic endpoints, the ability to perform activities of daily living, and important hemodynamic endpoints. However, given the site effects identified by the Agency, the Sponsor has submitted data from Study 306B.

6.1.2 Study 306B

Study 306 was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the clinical effect of droxidopa in PD patients with symptomatic nOH. The study included a Screening/Baseline Period (up to 14 days), an initial double-blind dose-titration

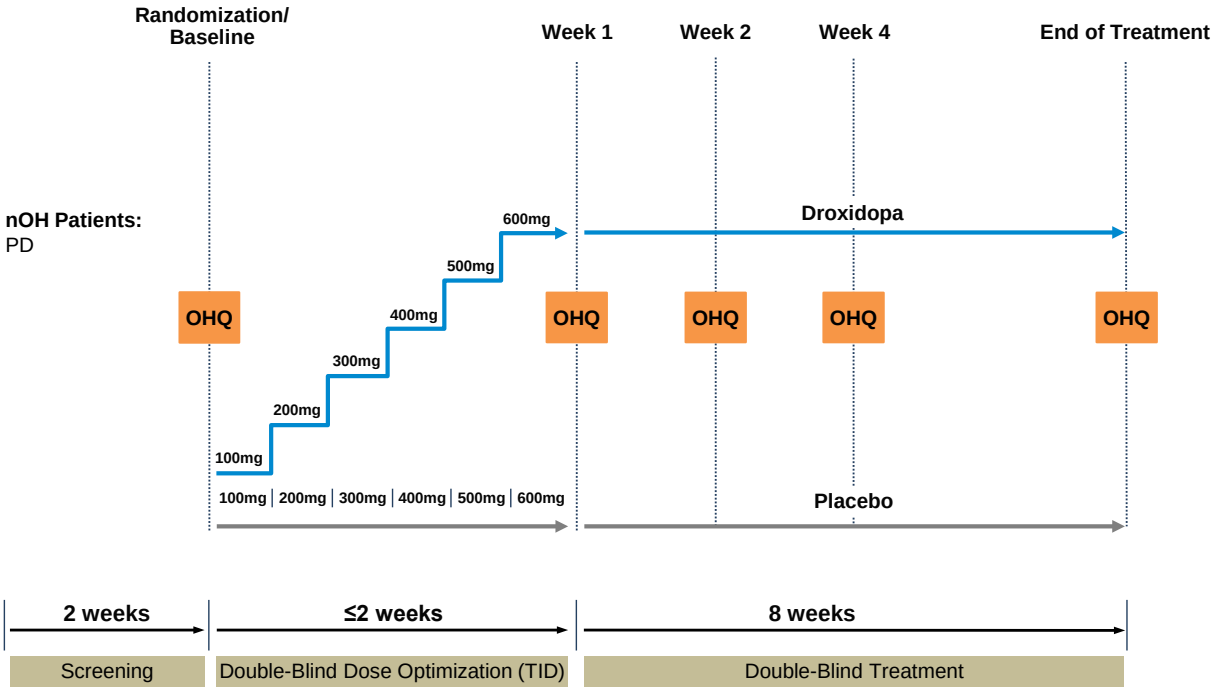
period (up to 14 days), an 8-week double-blind placebo-controlled treatment period, and a 2-week follow-up period.

The design of Study 306 is presented graphically in Figure 6-14 (see Appendix 2; Table 10-2 for a tabular summary of study results). The design of Study 306 differed from the design of Studies 301 and 302 in a number of ways. Study 306 enrolled only patients with PD with symptomatic nOH and only patients from the US, while Studies 301 and 302 enrolled patients with a variety of disease etiologies and symptomatic nOH from both US and non-US sites. Study 306 contained an 8-week randomized, placebo-controlled treatment phase to provide additional longer-term safety data and information on the durability of efficacy; in comparison, Studies 301 and 302 had randomized, placebo-controlled periods of 1 week and 2 weeks in duration, respectively. Finally, while Studies 301 and 302 both included open-label forced titration periods, Study 306 contained a double-blind forced titration period; the collection of placebo controlled comparative safety data during titration was an important objective for Study 306.

With regard to the double-blind dose optimization period, treatment was escalated in 100 mg TID increments until any one of the following titration stopping rules was met:

1. The patient became completely asymptomatic for symptoms of nOH as reported on the clinician-reported CGI-S (Defined as a score of 1 = Normal, no OH);
    - At the Investigator's discretion, dose escalation may have been stopped when a patient became nearly asymptomatic for symptoms of nOH on the clinician-reported CGI-S (Defined as a score of 2 = Borderline OH).
2. The patient had a SBP ≥180 mmHg or DBP ≥110 mmHg after 10 minutes in the supine position (head and torso elevated at approximately 30° from horizontal) which was replicated 2 more times (a total of 3 consecutive BP measurements in the supine position) over an hour;
    - At the Investigator's discretion dose escalation may have been stopped when a patient's BP was close to the limits defined above and further escalation was likely to result in BP levels exceeding the acceptable limit(s).
3. The patient was unable to tolerate side effects believed to be related to the study drug.
4. The patient reached a maximum dose of 600 mg TID.

Figure 6-14 Study 306: Study Design



nOH=Neurogenic Orthostatic Hypotension; OHQ=Orthostatic Hypotension Questionnaire; PD=Parkinson's Disease; TID=three times daily.

6.1.2.1 Interim Analysis and Primary Endpoint Change

Study 306 was originally powered based on a subgroup analysis of Study 302 (the only completed study at the time) which indicated that 84 PD patients would be sufficient to show a treatment benefit with droxidopa. Due to the limited data available for droxidopa overall, an interim analysis was prospectively included in Study 306 in order to review the safety and efficacy of the study. The safety data of all enrolled patients (N=113) and the efficacy data of the first 51 patients were included in the interim analysis in order to determine whether the study size of Study 306 needed to be increased.

During the interim analysis, the Data Monitoring Committee (DMC) only reviewed the primary endpoint: the mean change from Baseline to Week 8 in the OHQ composite score. After this review, the DMC recommended the trial be halted for futility. Enrollment was stopped, and the 51 patients who had been unblinded for the primary endpoint only were then fully unblinded, and all endpoints analyzed (62 patients had not yet completed the study, and their efficacy data remained blinded). This analysis showed indications of benefit across multiple endpoints, including dizziness/lightheadedness, reduction in patient falls, and increases in standing SBP. Based on these additional data, the DMC agreed that enrollment in the trial should resume. Consequently, Chelsea amended Study 306 and split the trial into separate parts, with each having separate hypotheses and SAPs. Patients included in the interim analysis were considered to be "Study 306A" patients, and patients enrolled after the interim analysis, as well as patients enrolled at the time of the interim analysis but not included in the interim analysis, were

considered as part of "Study 306B," which had intended to measure the reduction in patient falls as the primary endpoint.

Prior to the completion of Study 306B and after receiving a recommendation from the Agency to submit additional supportive data to the NDA, the protocol and SAP were amended, based partially on the Agency's feedback, to ultimately define the primary endpoint as the change in dizziness/lightheadedness (OHSA Item 1) from Baseline to Week 1 following 1 week of stable dose treatment. The target sample size was re-estimated, based on data from Study 301 (using PD patients only), to be 100 patients per arm (200 total) to demonstrate a difference of 1.1 units in the change in OHSA Item 1 from Baseline to Week 1 given a standard deviation of 2.8.

6.1.2.1.1 Maintenance of the Blind

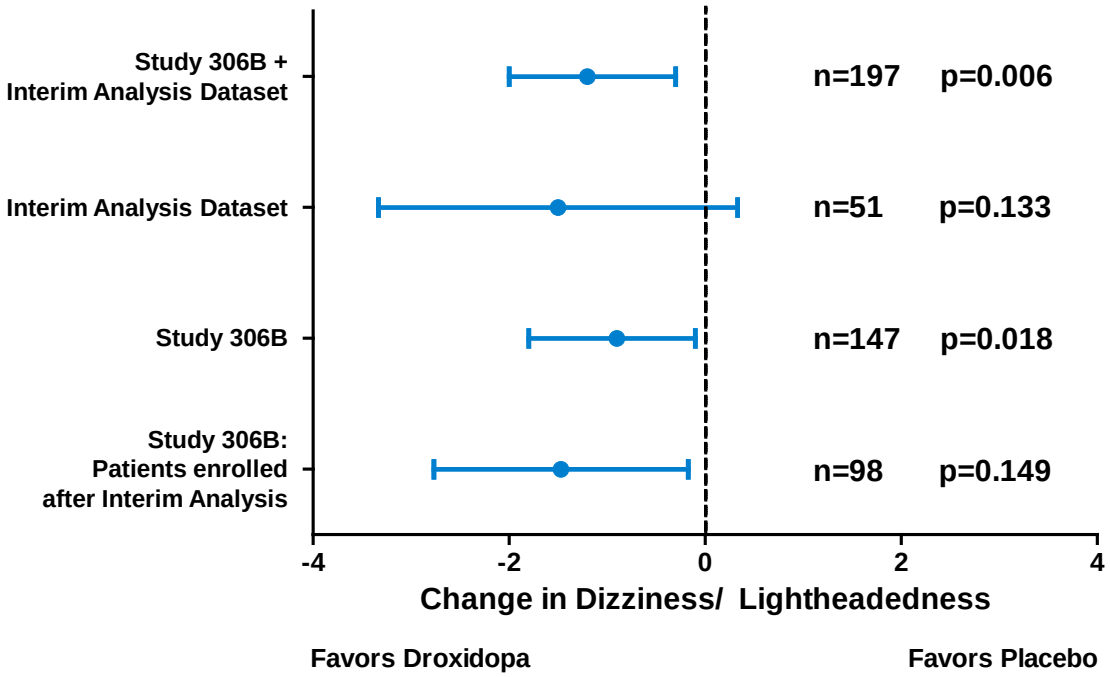
Firewalls and study procedures were in place to ensure that Chelsea remained at all times blinded to all data for patients in Study 306B until its completion. Detailed descriptions and summaries of the controls, Standard Operating Procedures, certifications, and other measures that were in place at the time of the changes in the primary endpoint and sample size to ensure Chelsea remained blinded to all data from Study 306B were submitted to FDA on 31 May 2012.

Firewalls and study procedures also prevented the unblinding of the Investigators as well as any patients not included in the interim analysis. The only results that were available to Investigators (and patients) were those included in a Press Release posted to the Chelsea website (http://www.chelseatherapeutics.com) on 02 February 2011; these top-line results needed to be released in order for the Sponsor to be in compliance with regulations for public companies.

However, the Agency indicated that there was a theoretical risk that the Sponsor could have become unblinded and, as noted above, the DCRP issued a General Advice Letter (29 June 2012) stating Study 306B was unlikely acceptable as a second positive study. Therefore, instead of reaching its target enrollment goal of 200 patients evaluable for efficacy, Chelsea prematurely terminated the study with only 147 patients. During the appeal to the Director of OND (see Section 5), the FDA conducted a further review of the blinding procedures and indicated it was likely that they were sufficient to protect the blinding of the study. The Director of OND reversed the General Advice Letter and stated that, subject to audits of the Sponsor and vendors, Study 306B has the potential to serve as a second positive study.

Of note, the Sponsor performed numerous sensitivity analyses comparing outcome measures for all patients in Study 306B compared with only those patients who had efficacy data entered after the interim analysis (Figure 6-15). No meaningful differences were observed between patients randomized prior to and after the interim analysis.

Figure 6-15 Study 306: Post-interim Analysis of Treatment Differences for OHSA Item 1 (FAS)



FAS=Full Analysis Set; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to change from Randomization were evaluated using non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for the Randomization value as a covariate.

In summary, there were adequate controls in place to prevent the Sponsor from being unblinded to the remaining patient data. There is no evidence that either the Sponsor or the Investigators were unblinded, and the interim analysis does not change the conclusions drawn from Study 306B.

6.1.2.2 Disposition, Demographics, and Concomitant Medications

6.1.2.2.1 Disposition

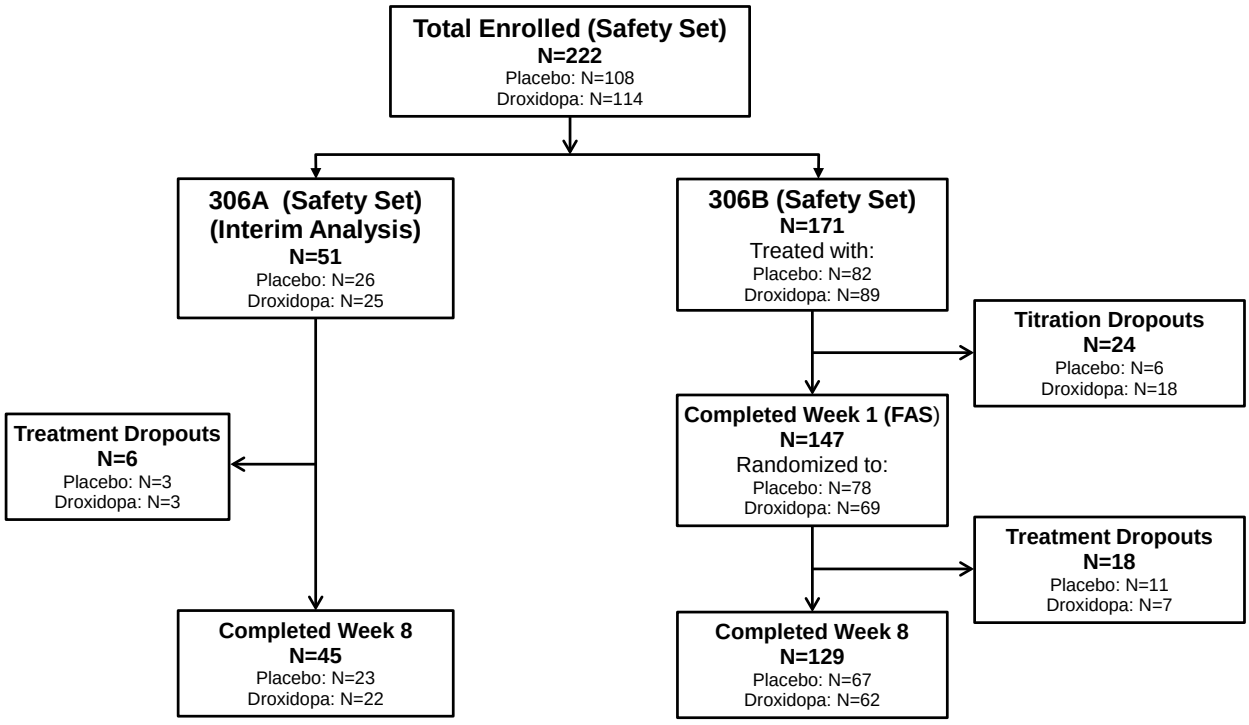
Overall, a total of 222 patients were enrolled into Study 306; 51 were assigned to Study 306A and 171 were assigned to Study 306B. Of the 171 patients assigned to Study 306B (and who comprise the Safety Set), 147 successfully completed the double-blind titration period and completed Week 1 of the double-blind treatment period (and comprise the FAS), and 24 patients were considered to be titration dropouts. Details regarding the reasons for dropouts during titration are provided in Section 6.1.2.7.

Of note, by the prospectively-defined rules of patient allocation for Study 306A, patients who had discontinued from Study 306A prior to completing titration were not to be included in the interim analysis; due to these rules, 8 patients who dropped out during titration in Study 306A

were assigned to Study 306B. An additional 16 patients from Study 306B were also titration failures.

Of the 147 patients who comprised the FAS (78 randomized to placebo and 69 randomized to droxidopa), a total of 129 patients (placebo, n=67; droxidopa, n=62), completed the entire 8-week treatment period (Figure 6-16).

Figure 6-16 Study 306: Overall Patient Disposition



FAS=Full Analysis Set.
Note: Three patients randomized to placebo inadvertently received at least one dose of droxidopa. These patients are included in the droxidopa arm for the safety set but in the placebo arm for all other disposition.

6.1.2.2.2 Demographics

Demographic characteristics were similar between the droxidopa and placebo treatment groups (Table 6-6). Study 306B was limited to patients in the US and enrolled only patients with a diagnosis of PD.

Table 6-6 Study 306B: Summary of Demographic and Baseline Characteristics (Safety Set)

	Placebo (N=82)	Droxidopa (N=89)
Sex [n (%)]		
Male	52 (63.4)	62 (69.7)
Female	30 (36.6)	27 (30.3)
Race [n (%)]		
White	79 (96.3)	85 (95.5)
Black/African American	1 (1.2)	2 (2.2)
Asian	0	1 (1.1)
Hispanic/Latino	2 (2.4)	1 (1.1)
Age (Years) at Screening		
Mean (SD)	72.0 (8.036)	72.5 (7.571)
Min, Max	52.9, 86.3	41.4, 91.7
Geographic Region [n (%)]		
US	82 (100)	82 (100)
Primary Clinical Diagnosis [n (%)]		
Parkinson's Disease	82 (100)	82 (100)
Baseline Disease Severity, n	78	69
Dizziness/Lightheadedness (Mean [range])	5.1 (0, 10)	5.1 (0, 9)
Lowest Mean SBP Between 0 and +3 minutes upon Standing (mmHg)		
Mean (SD)	95.7 (20.09)	94.7 (21.53)

FAS=Full Analysis Set; Max=maximum; Min=minimum; SBP=systolic blood pressure; SD=standard deviation.

Note: Demographic data are based on the Safety Set. Disease severity is the mean Baseline Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 Score and is based on the FAS.

6.1.2.2.3 Concomitant Medications

Overall, concomitant medication use was typical of the patient population and was similar between the droxidopa and placebo groups. All patients (100%) were taking concomitant medications (and were instructed to not change their concomitant medication use during the study).

The most commonly used concomitant medications were in the therapeutic area of the nervous system (98.8% and 97.8% of placebo-treated and droxidopa-treated patients, respectively). Sinemet (carbidopa/levodopa) was the most commonly used concomitant medication, which was taken by 65 (79.3%) placebo-treated and 70 (78.7%) droxidopa-treated patients.

Overall, concomitant medication use was typical of the patient population. With the exception of fludrocortisone, there were no clinically meaningful differences in concomitant medication use by therapeutic area or drug name observed between placebo-treated and droxidopa-treated

patients. There was a smaller proportion of placebo-treated patients taking concomitant fludrocortisone (19.5%) compared with droxidopa-treated patients (33.7%).

6.1.2.3 Dizziness (OHSA Item 1) and OHQ Composite Score

The evaluation of the primary endpoint, the OHSA Item 1 score (dizziness/lightheadedness), is summarized in Table 6-7 and displayed graphically in Figure 6-17. The mean change in the OHSA Item 1 score from Baseline to Week 1 showed statistically significant benefits favoring droxidopa (p=0.018). At Week 1, droxidopa-treated patients had a mean decrease from Baseline of 2.3 units in their OHSA Item 1 score (indicating improvement in the symptom of dizziness/lightheadedness) compared with a 1.3 unit decrease in placebo-treated patients, resulting in a treatment difference of 1.0 units favoring droxidopa.

In addition to the difference in favor of droxidopa on the primary endpoint, a treatment difference of 0.4 units in favor of droxidopa was observed for the OHQ composite score at Week 1, a difference that was not statistically significant (Table 6-7 and Figure 6-17).

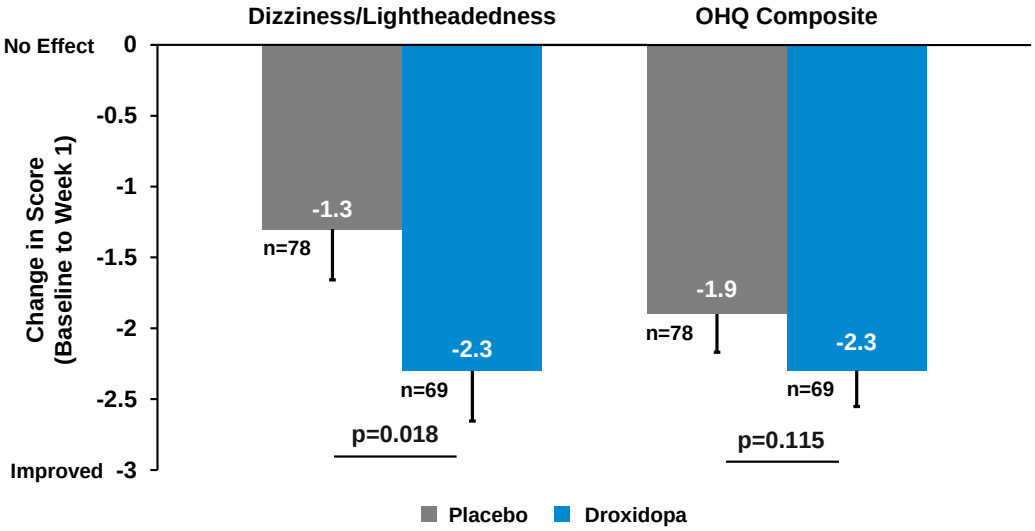
Table 6-7 Study 306B: Dizziness (OHSA Item 1) and OHQ Composite Scores at Week 1 (FAS, MDE)

	Placebo (N=78)		Droxidopa (N=69)			
Efficacy Endpoints	**n**	**Δ Mean (SD)**	**n**	**Δ Mean (SD)**	**Treatment Difference**	**p-value**
Primary Efficacy Endpoint						
OHSA Item 1 (dizziness/lightheadedness)	78	-1.3 (3.16)	69	-2.3 (2.95)	-1.0	0.018
Exploratory Endpoint						
OHQ Composite Score	78	-1.9 (2.39)	69	-2.3 (2.12)	-0.4	0.115

ANCOVA=Analysis of covariance; Δ=Change; FAS=Full Analysis Set; MDE=missing data excluded; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SD=Standard deviation.

Note: Since the assumptions for the ANCOVA (independence, constant variance, or normality of the residuals) were not met for OHSA Item 1, the efficacy endpoint analysis was based on non-parametric methodology which used Cochran-Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate (OHSA Item 1 at Baseline). For the OHQ, treatment differences were tested using a parametric ANCOVA with effects for treatment and Baseline value.

Figure 6-17 Study 306B: Dizziness (OHSA Item 1) and OHQ Composite Score (FAS, MDE)

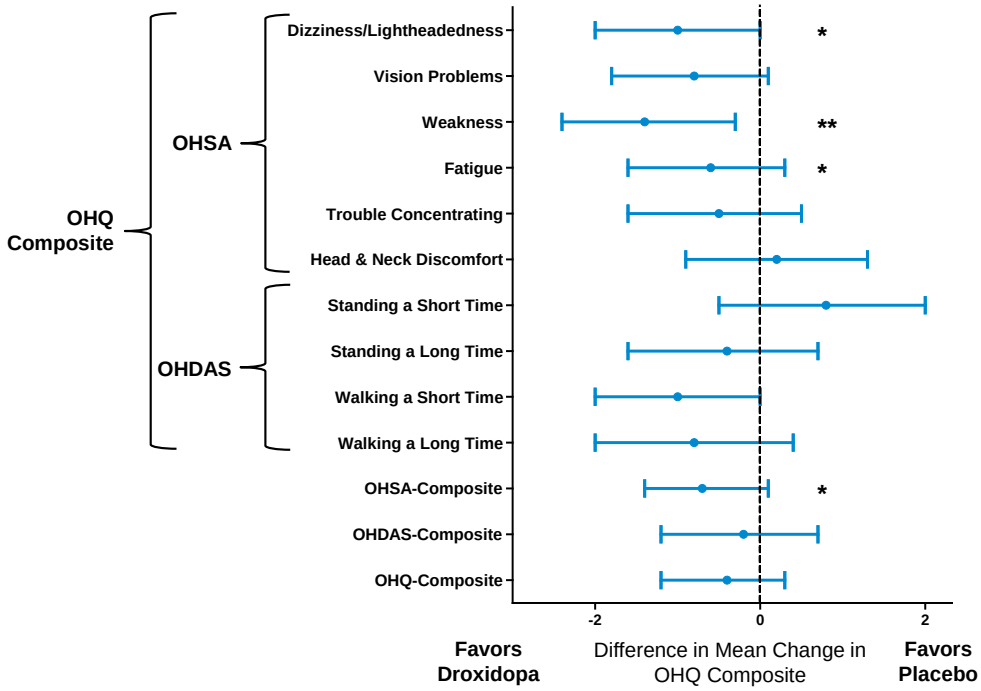


ANCOVA=analysis of covariance; FAS=Full Analysis Set; MDE=missing data excluded; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: Since the assumptions for the ANCOVA (independence, constant variance, or normality of the residuals) were not met for OHSA Item 1, the efficacy endpoint analysis was based on non-parametric methodology which used Cochran-Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate (OHSA Item 1 at Baseline). For the OHQ, treatment differences were tested using a parametric ANCOVA with effects for treatment and Baseline value.

Similar to the results from Studies 301 and 302, droxidopa-treated patients in Study 306B experienced consistent benefits across a broad range of other symptoms as well as the impact of these symptoms on their ability to perform activities of daily living (Figure 6-18). Droxidopa-treated patients showed statistically significant improvements versus placebo on 3 of the 6 individual symptom scores of the OHSA (including dizziness/lightheadedness) as well as the OHSA composite score; numerical improvements were observed on 8 of the 10 individual components of the OHQ. The improvements observed across the multiple individual items of the OHQ demonstrate the short-term benefits of droxidopa.

Figure 6-18 Study 306B: Treatment Differences for OHQ Components (FAS, MDE)



ANCOVA=analysis of covariance; FAS=Full Analysis Set; MDE=missing data excluded; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

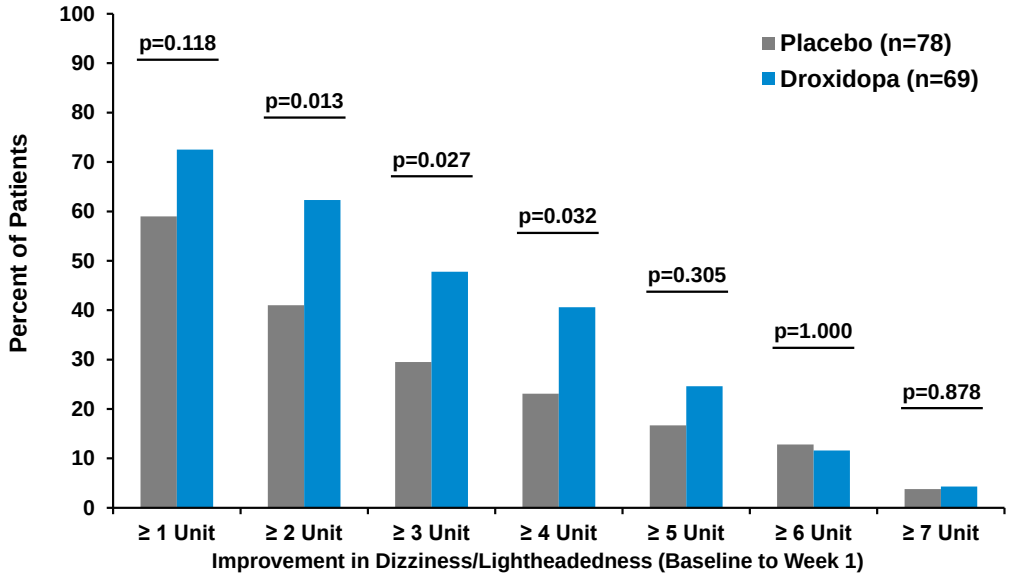
Note: If assumptions for the ANCOVA (independence, constant variance, or normality of the residuals) were not met, the efficacy endpoint analysis was based on non-parametric methodology which used Cochran-Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate (OHSA Item 1) (*p<0.05; **p<0.01). Confidence intervals are not adjusted for covariates and may cross the zero line despite statistical significance.

6.1.2.3.1 Evidence of Efficacy from Multiple Supportive Analyses

Responder Analyses of OHSA Item 1

Similar to results observed in Study 301, a *post-hoc* analysis of Study 306B revealed treatment differences in favor of droxidopa based on unit improvements from Baseline to Week 1 in the OHSA Item 1 score for the ≥1-, 2-, 3-, 4-, and 5-unit improvement categories (Figure 6-19).

Figure 6-19 Study 306B: Dizziness (OHSA Item 1) Responders Analysis (FAS, MDE)

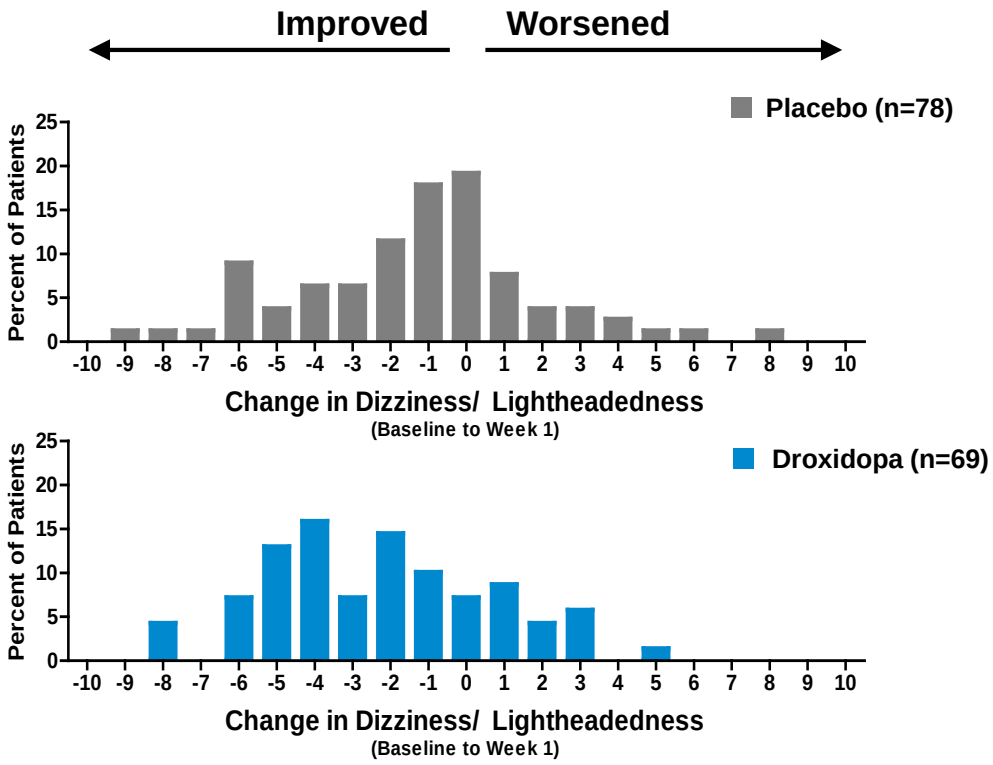


FAS=Full Analysis Set; MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Treatment differences tested using Fisher's Exact Test.

Bin Analyses of OHSA Item 1

In Study 306B, when patients are grouped according to their actual dizziness response and each patient is only included once, more droxidopa-treated patients experienced improvements and fewer droxidopa-treated patients worsened compared with placebo-treated patients in the OHSA Item 1 score from Baseline to Week 1 (Figure 6-20).

Figure 6-20 Study 306B: Distribution of Changes in the Dizziness (OHSA Item 1) Score (FAS, MDE)

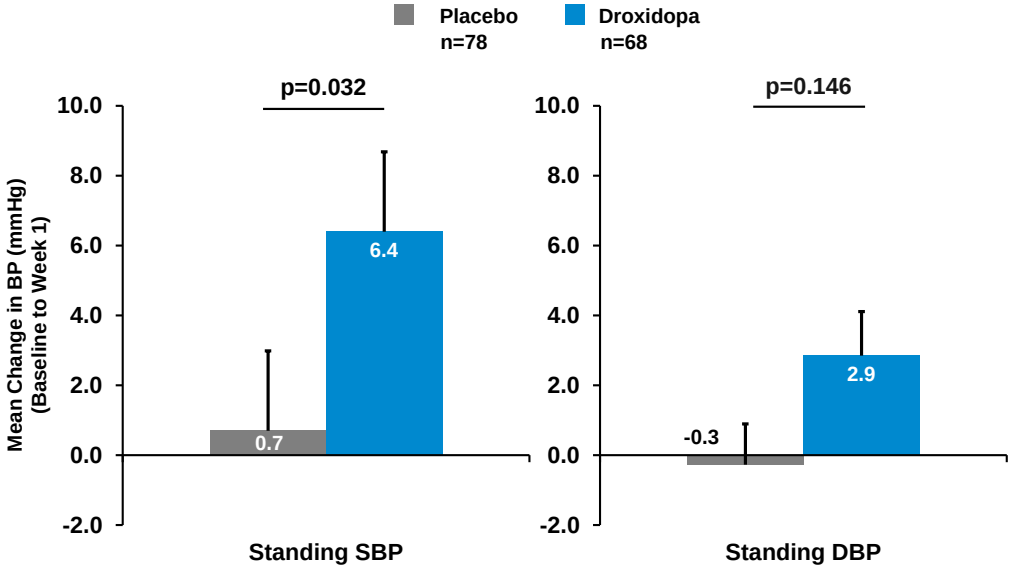


FAS=Full Analysis Set; MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment.

6.1.2.4 Standing Blood Pressure Response at Week 1

Similar to Study 301, Study 306B was not specifically designed to capture benefits in BP (although change in standing BP was a pre-specified secondary efficacy endpoint). Nevertheless, patients experienced a significant change from Baseline to Week 1 in standing SBP compared with placebo: mean change in standing SBP of 6.4 mmHg following treatment with droxidopa compared with 0.7 mmHg following treatment with placebo (p=0.032), resulting in a difference between placebo and droxidopa of 5.7 mmHg favoring droxidopa (Figure 6-21). Treatment with droxidopa also resulted in numerically superior improvements in standing DBP from Baseline to Week 1 compared with placebo.

Figure 6-21 Study 306B: Increase in Standing Blood Pressure (FAS, MDE)



ANCOVA=analysis of covariance; BP=blood pressure; DBP=diastolic blood pressure; FAS=Full Analysis Set; MDE=missing data excluded; SBP=systolic blood pressure.

Note: The differences between placebo and droxidopa with respect to changes from Baseline were evaluated using non-parametric ANCOVA using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for the Baseline value as a covariate for SBP, and using Wilcoxon Rank Sum test for DBP.

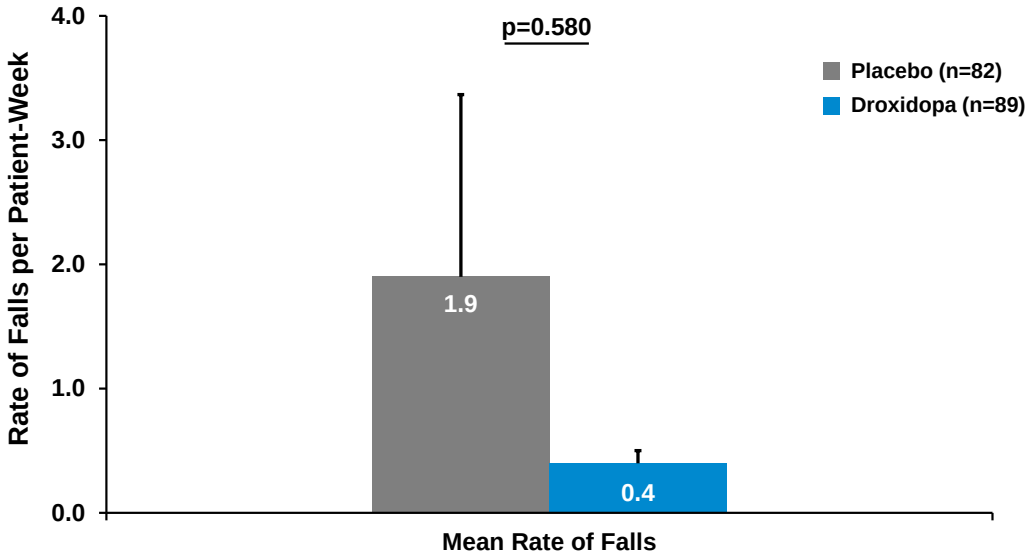
6.1.2.5 Falls and Fall-Related Injuries

While falls may occur due to a variety of conditions within patients, it is clear that nOH is associated with an increased incidence of falls. Evidence of a reduction in the rate of falls is highly likely to be supportive of droxidopa's effectiveness for the treatment of nOH. Furthermore, a reduction in the number of patients with fall-related injuries is an independent, objective measure of a meaningful, clinical benefit.

Studies 301 and 302 had more patients reporting a TEAE of fall in the placebo group (n=9) compared with the droxidopa group (n=1). This observation, given the short (1- to 2-week) duration of those studies and the spontaneous nature of the reporting, led to the decision to prospectively collect data on falls via electronic patient diaries in both Studies 306A and 306B. The definition of a "fall" in Study 306 was similar to others commonly used and accepted as standard in the field which was "unexpectantly coming to rest on the ground, floor, or just a lower level than where you started."

Data demonstrating that patients treated with droxidopa experience a lower rate of falls compared with those treated with placebo are shown in Figure 6-22 below. The mean rate of patient falls per patient-week was lower in the droxidopa group (0.4) compared with the placebo group (1.9); this difference was not statistically significant.

Figure 6-22 Study 306B: Mean Rate of Patient-Reported Falls per Week (Safety Set, MDE)



MDE=missing data excluded; SEM=standard error of the mean.
Note: Patient rate of falls is calculated for each patient as the (total number of falls/number of evaluable days)*7. All study populations are Safety Set with MDE. SEM is presented for mean rate of falls per patient week. Results tested using Wilcoxon rank sum test.

Patients in the droxidopa group also experienced a lower number of total falls during treatment (246 falls) compared with the placebo group (715 falls) (Table 6-8). The difference in the number of falls was evident as early as the end of titration, at which time there were 61 total falls in the droxidopa group and 232 falls in the placebo group.

Table 6-8 Study 306B: Patient-Reported Falls (Safety Set, MDE)

Analysis	Placebo (N=81)[1]	Droxidopa (N=87)[1]
Number of Falls, n	715	246
Cumulative Count of Falls[2], n		
By End of Titration	232	61
By Week 1	391	92
By Week 2	498	117
By Week 4	585	157
By Week 8	715	246
Patients with ≥1 Fall[3], n (%)	46 (56.8)	45 (51.7)
Mean (SD) Patient Rate of Falls Per Patient-Week[4]	1.9 (12.71)	0.4 (1.10)

MDE=missing data excluded; SD=standard deviation.
Note: Safety Set with MDE is presented.
1 All subjects had evaluable records defined as any non-missing response in the daily falls diary.
2 Number of falls by each week is cumulative (i.e., a patient who fell during Week 1 also fell by Week 2).
3 Percentages are based on the number of patients with any evaluable record.
4 Patient rate of falls is calculated for each patient as the (total number of falls/number of evaluable days)*7.

Despite the large absolute differences in the number and rate of falls between droxidopa-treated and placebo-treated patients, the results were not statistically significant. The large number of patients who did not fall (approximately 40%) combined with the wide distribution in the number of falls among patients, both of which made for difficulties in the statistical modeling and testing for falls, likely explains the lack of statistical significance.

Fall-related injuries were prospectively defined as traumatic injuries occurring within 24 hours of a fall as captured in daily patient fall diaries. A fall-related injury was defined as a pre-defined AE occurring on the day of, or the day after, a reported fall; all relevant preferred terms for fall-related injuries were prospectively identified. As shown in Table 6-9 below, a lower proportion of patients treated with droxidopa experienced a fall-related injury (16.9%) compared with patients treated with placebo (25.6%). Falls also resulted in potentially debilitating TEAEs, including facial bones fracture, fibula fracture (serious AE [SAE]), and traumatic brain injury in a total of 3 placebo-treated patients compared with 0 droxidopa-treated patients.

Table 6-9 Study 306B: TEAEs Related to Falls (Safety Set)

	Placebo (N=82)		Droxidopa (N=89)	
	n (%)	E	n (%)	E
Number of Patients (%) and Number of TEAEs Related to Falls	**21 (25.6%)**	**35**	**15 (16.9%)**	**24**
Injury, poisoning, and procedural complications	**21 (25.6)**	**33**	**12 (13.5)**	**18**
Excoriation	7 (8.5)	7	5 (5.6)	5
Contusion	10 (12.2)	12	3 (3.4)	4
Skin laceration	7 (8.5)	7	3 (3.4)	6
Laceration	1 (1.2)	1	2 (2.2)	2
Injury	1 (1.2)	1	1 (1.1)	1
Facial bones fracture	1 (1.2)	1	0	0
Fall	1 (1.2)	1	0	0
Fibula fracture	1 (1.2)	1	0	0
Joint sprain	1 (1.2)	1	0	0
Traumatic brain injury	1 (1.2)	1	0	0
General disorders and administration site conditions	**0**	**0**	**3 (3.4)**	**3**
Pain	0	0	2 (2.2)	2
Face oedema	0	0	1 (1.1)	1
Musculoskeletal and connective tissue disorders	**2 (2.4)**	**2**	**2 (2.2)**	**2**
Arthralgia	1 (1.2)	1	1 (1.1)	1
Back pain	1 (1.2)	1	1 (1.1)	1
Eye disorders	**0**	**0**	**1 (1.1)**	**1**
Conjunctival haemorrhage	0	0	1 (1.1)	1

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Events are counted each time in the event (E) column. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0.

6.1.2.6 Clinical Global Impressions of Severity and Improvement

At Week 1, greater improvements (i.e., decreases) from Baseline in the mean clinician-reported CGI-S scores were observed in the droxidopa group compared with the placebo group, resulting in a treatment difference from placebo of 0.4 units favoring droxidopa. The treatment difference at Week 1 was statistically significant (p=0.025) (Appendix 9; Table 10-15).

With regard to the patient-reported CGI-S scores, a comparatively smaller numerical improvement from Baseline to Week 1 in the mean CGI-S scores was observed in the droxidopa group compared with the placebo group (treatments difference of 0.3).

At Week 1, a greater improvement in the mean clinician-reported CGI-I scores was observed in the droxidopa group compared with the placebo group, resulting in a statistically significant

treatment difference from placebo of 0.5 units favoring droxidopa (p=0.009; Appendix 9; Table 10-16). In addition to improvements in the absolute CGI-I scores, a higher percentage of patients in the droxidopa group were reported as being "very much to slightly improved" at Week 1 (73.9%) compared with placebo (58.4%).

With regard to the patient-reported CGI-I scores, a comparatively smaller numerical improvement in the mean CGI-I scores was observed in the droxidopa group compared with the placebo group (0.2 units; Appendix 9; Table 10-16). Similar to the clinician-reported CGI-I scores, a higher percentage of patients in the droxidopa group were reported as being "very much to slightly improved" at Week 1 (71.0%) compared with placebo (58.4%).

6.1.2.7 Sensitivity Analyses

6.1.2.7.1 Titration Dropouts

The primary analysis of the primary endpoint of Study 306B included a pre-defined analysis population which excluded patients who discontinued prior to Week 1. A total of 24 patients dropped out prior to Week 1 and, therefore, were not included in the pre-defined analysis population. Of these 24 patients, there were more discontinuations in the droxidopa group (n=18) compared with the placebo group (n=6). Table 6-10 provides a summary of the Investigator-determined reason these 24 patients discontinued prior to Week 1.

Table 6-10 Study 306B: Reasons for Titration Dropouts

Investigator-determined Reasons for Dropout	Placebo (N=6) n (%)	Droxidopa (N=18) n (%)
Total Dropouts	**6**	**18**
AE- or BP-related	4 (66.6)	6 (33.3)
Other	2 (33.3)	2 (11.1)
Patient Withdrew Consent	0	3 (16.7)
Lack of Efficacy	0	3 (16.7)
Treatment Failure	0	1 (5.6)
Investigator Decision	0	2 (11.1)
Protocol Violation	0	1 (5.6)

AE=adverse event; BP=blood pressure.

In general, there was no particular TEAE or other reason driving patient discontinuations in the droxidopa treatment arm compared with placebo (Table 6-11). Additionally, for patients who discontinued for reasons other than TEAEs or BP-related events, there was no consistent reason for these discontinuations, which included a patient who failed to meet entry criteria and a patient who did not complete titration during the pre-specified period.

In addition, one site (Site 183) accounted for 4 dropouts, all of whom were on the highest dose of droxidopa, did not experience TEAEs, and completed titration. By completing titration, all 4 patients met the minimum eligibility requirements for the long-term open-label extension study which they all immediately entered and continued on droxidopa therapy. Two of these patients

were on droxidopa for nearly 1 year by the time the study was terminated. This observation was detected during the course of the study and immediate corrective actions were taken.

Table 6-11 Study 306B: Per Patient Reasons for Titration Dropouts

Treatment	Patient	Investigator-Determined Discontinuation Reason	Additional Details from CRF
Placebo	160005	Adverse Event	Blood Pressure Increased
Placebo	122014	Other	Subject's Blood Pressure Over 180 mmHg
Placebo	112004	Other	Investigator Decision Due to Borderline Blood Pressure
Placebo	110006	Adverse Event	Atrial fibrillation
Placebo	176003	Adverse Event	Gastroenteritis
Placebo	161005	Adverse Event	Malaise
Droxidopa	113008	Other	Supine Hypertension
Droxidopa	132004	Adverse Event	Supine Hypertension
Droxidopa	184003	Adverse Event	Exacerbation of Hypertension
Droxidopa	156002	Adverse Event	Worsening of Elevated Blood Pressure
Droxidopa	152004	Adverse Event	Exacerbation of Hypotension
Droxidopa	182008	Adverse Event	Worsening of Parkinson's
Droxidopa	115004	Adverse Event	Worsening of Hallucination (Medical history >3 years hallucinations; titration was stopped as patient was considered "nearly asymptomatic")
Droxidopa	164005	Patient Withdrew Consent	Patient reported a number of mild AEs including nausea, headache, worsening of PD, diarrhea, and common cold;
Droxidopa	110004	Patient Withdrew Consent	No additional information included in the CRF
Droxidopa	140001	Patient Withdrew Consent	Lack of efficacy (Subject withdrew from study for intolerable orthostatic symptoms)
Droxidopa	132010	Lack of Efficacy	Patient completed all titration visits
Droxidopa	183007[1]	Lack of Efficacy	Patient was deemed treatment failure after receiving 2 days of study drug during the maintenance phase
Droxidopa	183008[1]	Lack of Efficacy	Patient was deemed treatment failure after receiving 1 week of study drug during the maintenance phase
Droxidopa	183002[1]	Treatment Failure	Patient was deemed treatment failure after receiving 1 day of study drug during the maintenance phase
Droxidopa	183009[1]	Investigator Decision	Site initially listed reason as treatment failure but changed reason to Investigator Decision
Droxidopa	142003	Other	Patient unable to finish titration visit before allotted time frame
Droxidopa	118004	Investigator Decision	Patient withdrawn due to lack of compliance with study medication
Droxidopa	160001	Protocol Violation	Patient determined post-randomization to not meet entry criteria on OHQ

AE=adverse event; BP=blood pressure; CRF=case report form; OHQ=Orthostatic Hypotension Questionnaire; PD=Parkinson's Disease.

1 These patients were enrolled at Site 183.

The Sponsor recognizes that early discontinuations may introduce bias for a variety of reasons. The primary analysis of the primary endpoint is a completers analysis and must be evaluated

within the context of other analyses on the ITT population. There is not a set rule or standard on the best method of data imputation for missing data such as from these 24 patients. Thus, the Sponsor performed a series of sensitivity analyses to evaluate the robustness of the primary efficacy results. Summaries of these analyses are provided below.

As indicated above, the analysis set used for the primary analysis of Study 306B (N=147) was prospectively described in the SAP as all patients who received at least one dose of drug and had efficacy data collected at Baseline and Week 1.

The population used for the sensitivity analyses (N=171) is composed of all patients who were randomized into the study and received at least one dose of study drug at any time during the study. Of note, discontinuations during titration were assigned to Study 306B due to data handling rules at the interim analysis. This had the unintended consequence of inflating the rate of patient discontinuations in Study 306B by 8 patients.

6.1.2.7.1.1 Mean Change OHSA Item 1 (ITT)

To evaluate the robustness of the primary efficacy results, the Sponsor applied the following imputation techniques to the sensitivity analysis dataset (N=171 [ITT Population]). Of the 24 patients excluded from the primary analysis, 16 patients had an Early Termination Visit (ETV). For 8 of 16 ETVs, patients were off drug for a range of 1 to 12 days. Data have been imputed for the 8 patients with no post-Baseline efficacy measurements. Otherwise, the data from the ETV are used. Of note, the analyses using the following imputation techniques were completed *post-hoc*.

Worst Case: For OHSA Item 1, for the 8 patients with no post-Baseline efficacy measurements, those on droxidopa were assumed to have the worst possible outcome at Visit 4 (10 units) and those on placebo were assumed to have the best possible outcome (0 units).

LOCF (Last Observation Carried Forward): For OHSA Item 1, for the 8 patients with no post-Baseline efficacy measurements, the value at Baseline was carried forward to Week 1.

MMRM1: a mixed-model repeated measures (MMRM) analysis of information from the observed data which is used via a within-patient correlation structure to provide information about the unobserved data, but the missing data are not explicitly imputed. The OHSA Item 1 values at Baseline are considered as an outcome variable and assigned as a placebo treatment. Only ETV values from patients who completed titration are used in the analysis.

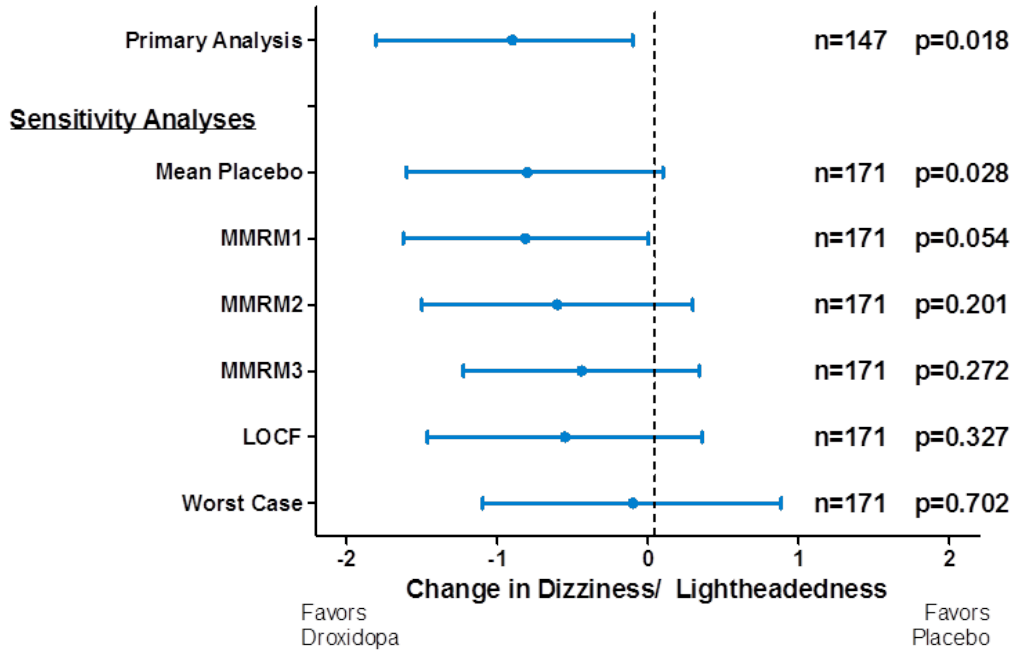
***MMRM2*:** an MMRM analysis of information from the observed data which is used via a within-patient correlation structure to provide information about the unobserved data, but the missing data are not explicitly imputed. The OHSA Item 1 values at Baseline are used as a co-factor in determining the treatment effect. All ETV values are used in the analysis.

MMRM3: an MMRM analysis of information from the observed data which is used via a within-patient correlation structure to provide information about the unobserved data, but the missing data are not explicitly imputed. The OHSA Item 1 values at Baseline are considered as an outcome variable and assigned as a placebo treatment. All ETV values are used in the analysis.

Mean Placebo: For OHSA Item 1, for patients who did complete a Week 1 visit, the Sponsor imputed missing data using the mean response from Baseline to Week 1 taken from the placebo arm of the primary analysis population.

As shown in Figure 6-23, while Study 306B loses statistical significance when various sensitivity analyses are performed using different imputation techniques, all analyses show that the point estimates favor droxidopa treatment over placebo on the mean change from Baseline at Week 1 in the OHSA Item 1 score.

Figure 6-23 Study 306B: Treatment Differences for OHSA Item 1 (ITT)



ITT=Intent-to-treat; LOCF=last observation carried forward; MMRM=mixed-model repeated measures; OHSA=Orthostatic Hypotension Symptom Assessment.

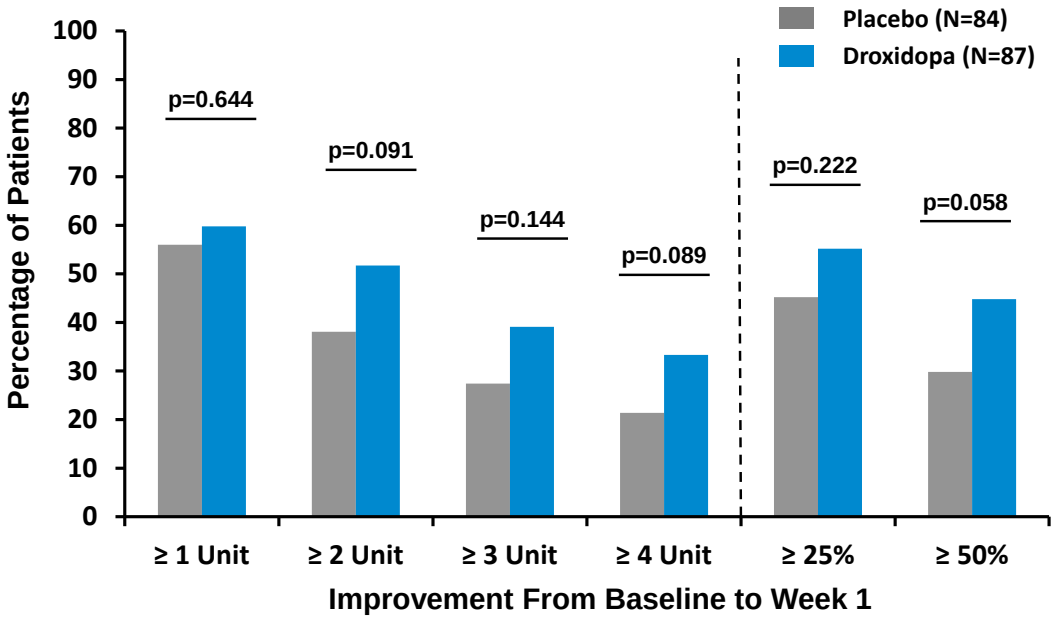
Note: Assumptions for data imputation are discussed above. Confidence intervals are not adjusted for covariates and may cross the zero line despite statistical significance.

6.1.2.7.1.2 Responder Analyses (ITT)

In trials with significant amounts of missing data, responder analyses may represent the most meaningful way of investigating the existence of a treatment effect (European Medicines Agency Guideline on Missing Data in Confirmatory Clinical Trials). Figure 6-24 presents data from Study 306B. The results from these *post-hoc* analyses demonstrate that, even when patients who

discontinued during titration are included in the analyses as "non-responders," there remains a subset of patients who benefit from droxidopa treatment across a range of responses.

Figure 6-24 Study 306B: OHSA Item 1 Responder Analysis (ITT; N=171)

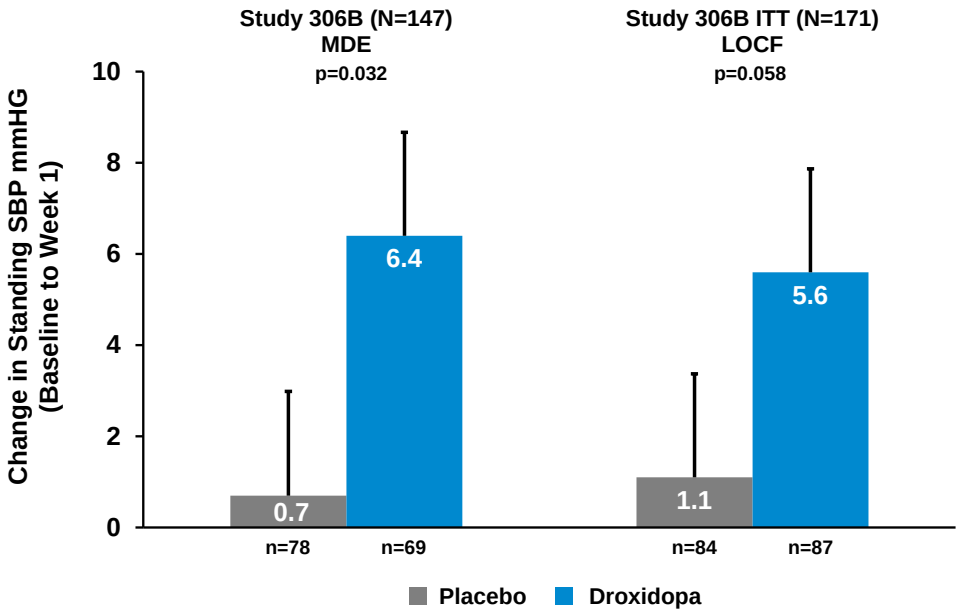


ITT=Intent-to-treat; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Patients with missing data were categorized as non-responders. Treatment differences were tested using Fisher's Exact Test.

6.1.2.7.1.3 Blood Pressure (ITT)

Blood pressure was to be collected at all titration visits by the OST. Therefore, all patients (with one exception, Patient 164005, for whom the Baseline observation was carried forward) have a post-Baseline standing BP measurement. Figure 6-25 below compares the primary analysis population from Study 306B (N=147) versus the ITT population from Study 306B (N=171). In both of these analyses, treatment with droxidopa resulted in larger increases from Baseline to Week 1 in standing SBP compared with placebo.

Figure 6-25 Study 306B: Standing Systolic SBP Mean Changes from Baseline to Week 1



ITT=Intent-to-treat; LOCF=last observation carried forward; MDE=missing data excluded; SBP=systolic blood pressure.
Note: Data imputed as LOCF including early termination visits.
Note: p-values presented are from non-parametric Cochran-Mantel-Haenszel analysis.

6.1.2.7.2 Conclusions on Site Effects in Study 306B

Study 306B loses statistical significance after removal of the largest (n=18, [12.2%]) and best-performing site (Site 132). However, sensitivity analyses show that data from this site are consistent with responses seen in the broader study. There were no anomalous characteristics in terms of clustering or overlap in the distribution of responses at this site and the loss of statistical significance upon exclusion of Site 132 is likely due to the reduced sample size available for analysis.

6.1.2.8 Efficacy Conclusions from Study 306B

The results from Study 306B are strongly supportive of Study 301 and show that droxidopa provides short-term benefits in the treatment of symptomatic nOH. In addition, results from Study 306B suggest that droxidopa was associated with a reduction in falls and fall-related injuries.

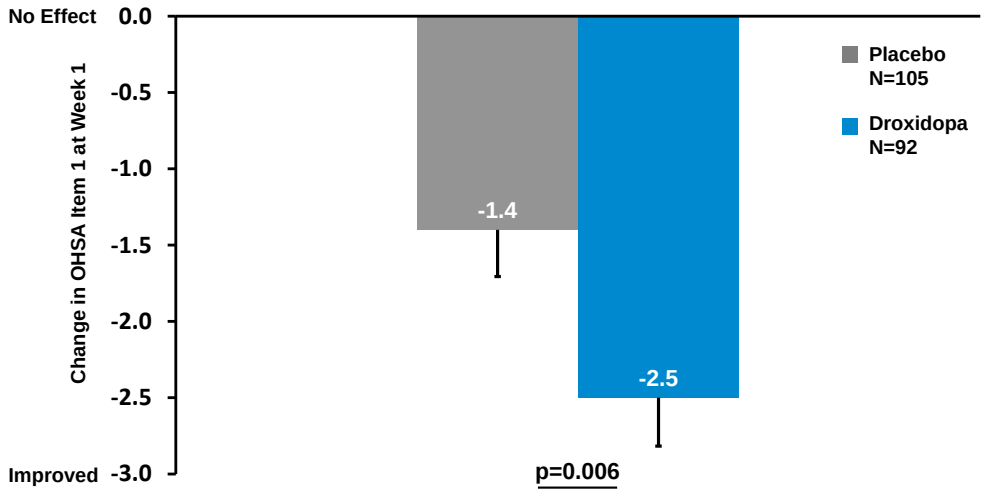
6.1.3 Study 306B and the Interim Analysis Dataset

To further confirm the robustness of the results from Study 306B, the 51 patients from the Interim Analysis Dataset (Study 306A) were combined with the patients from Study 306B.

6.1.3.1 Dizziness (OHSA Item 1)

Similar to the results from Study 306B alone, the mean change in the OHSA Item 1 score from Baseline to Week 1 for the Study 306B+Interim Analysis Dataset showed benefits favoring droxidopa (p=0.006; Figure 6-26). At Week 1, droxidopa patients had a mean decrease from Baseline of 2.5 units in their OHSA Item 1 score (indicating improvement in the symptom of dizziness/lightheadedness) compared with a 1.4 unit decrease in placebo patients, resulting in a treatment difference of 1.1 units favoring droxidopa.

Figure 6-26 Study 306B+Interim Analysis Dataset: Effect on Dizziness (OHSA Item 1) at Week 1 (FAS, MDE)

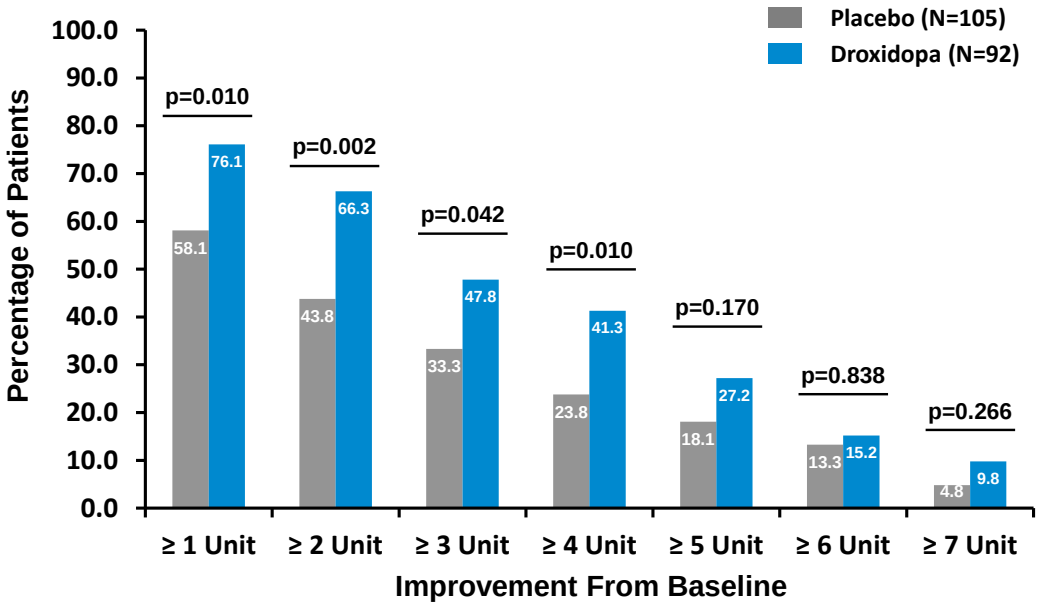


ANCOVA=analysis of covariance; FAS=Full Analysis Set; MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: Since the assumptions for the ANCOVA (independence, constant variance, or normality of the residuals) were not met, the efficacy endpoint analysis was based on non-parametric methodology which used Cochran-Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate (OHSA Item 1). Treatment differences tested using a non-parametric ANCOVA with effects for treatment and Baseline value.

Results from responder analyses for the Study 306B+Interim Dataset were consistent with Study 306B. At Week 1, higher percentages of patients in the droxidopa group met dizziness (OHSA Item 1) responder criteria based on unit improvements from Baseline compared with the placebo group across all unit improvement categories (Figure 6-27).

Figure 6-27 Study 306B+Interim Analysis Dataset: Dizziness (OHSA Item 1) Responders at Week 1 Analysis (FAS, MDE)

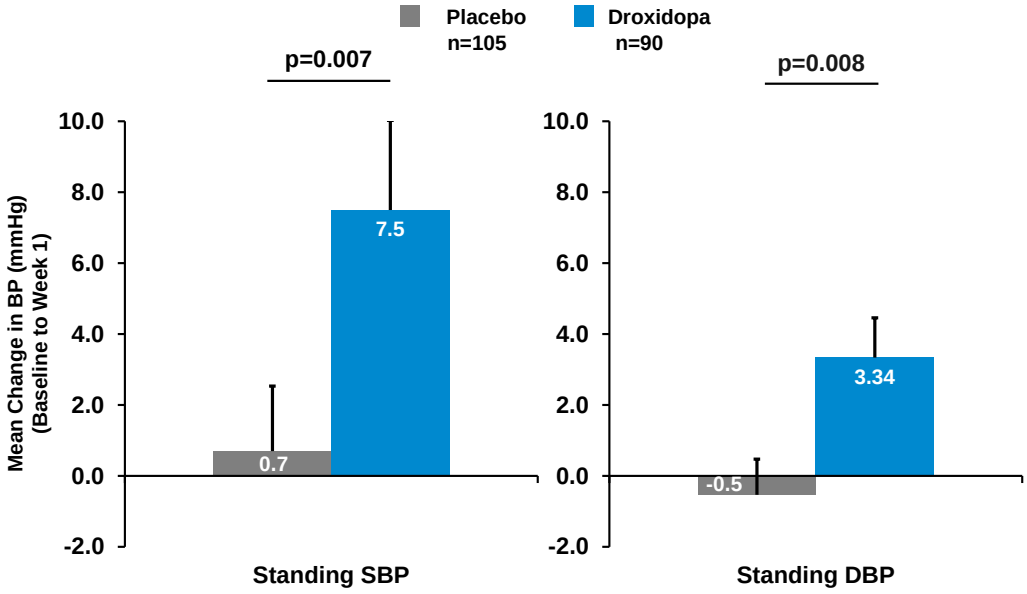


FAS=Full Analysis Set; MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Treatment differences tested using Fisher's Exact Test.

6.1.3.2 Standing Blood Pressure Response at Week 1

Similar to the results from Study 306B, patients in the Study 306B+Interim Analysis Dataset receiving droxidopa experienced a larger change from Baseline to Week 1 in standing SBP compared with placebo: mean change in standing SBP of 7.5 mmHg following treatment with droxidopa compared with 0.7 mmHg following treatment with placebo, resulting in a difference between placebo and droxidopa of 6.8 mmHg favoring droxidopa (p=0.007; Figure 6-28). In addition, larger improvements in standing DBP from Baseline to Week 1 were also observed in the Study 306B+Interim Analysis Dataset (droxidopa: +3.34 mmHg; placebo: -0.53 mmHg; p=0.008).

Figure 6-28 Study 306B+Interim Dataset: Standing Systolic Blood Pressure at Week 1 (FAS, MDE)

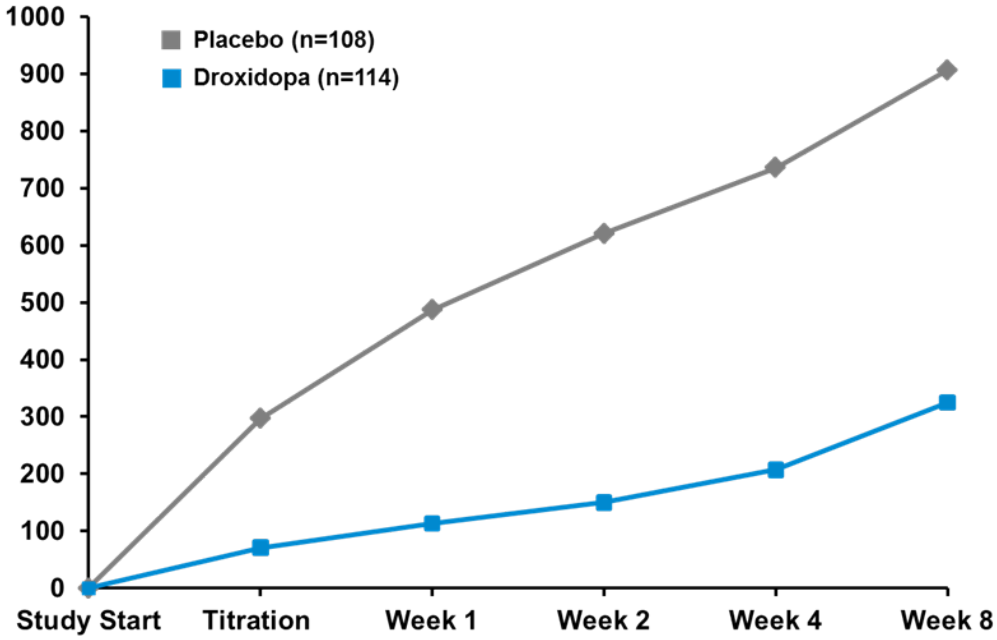


BP=blood pressure; DBP=diastolic blood pressure; FAS=Full Analysis Set; MDE=missing data excluded; SBP=systolic blood pressure.
Treatment differences tested using a non-parametric ANCOVA with effects for treatment and Baseline value.

6.1.3.3 Cumulative Falls

Similar to Study 306B, data from the Study 306B+Interim Analysis Dataset demonstrated that patients in the droxidopa group experienced a lower number of total falls during treatment (325 falls) compared with the placebo group (907 falls; Figure 6-29). This decrease in falls is an important potential benefit for droxidopa which will be evaluated in future studies.

Figure 6-29 Study 306B+Interim Dataset: Mean Cumulative Falls (Safety Set, MDE)

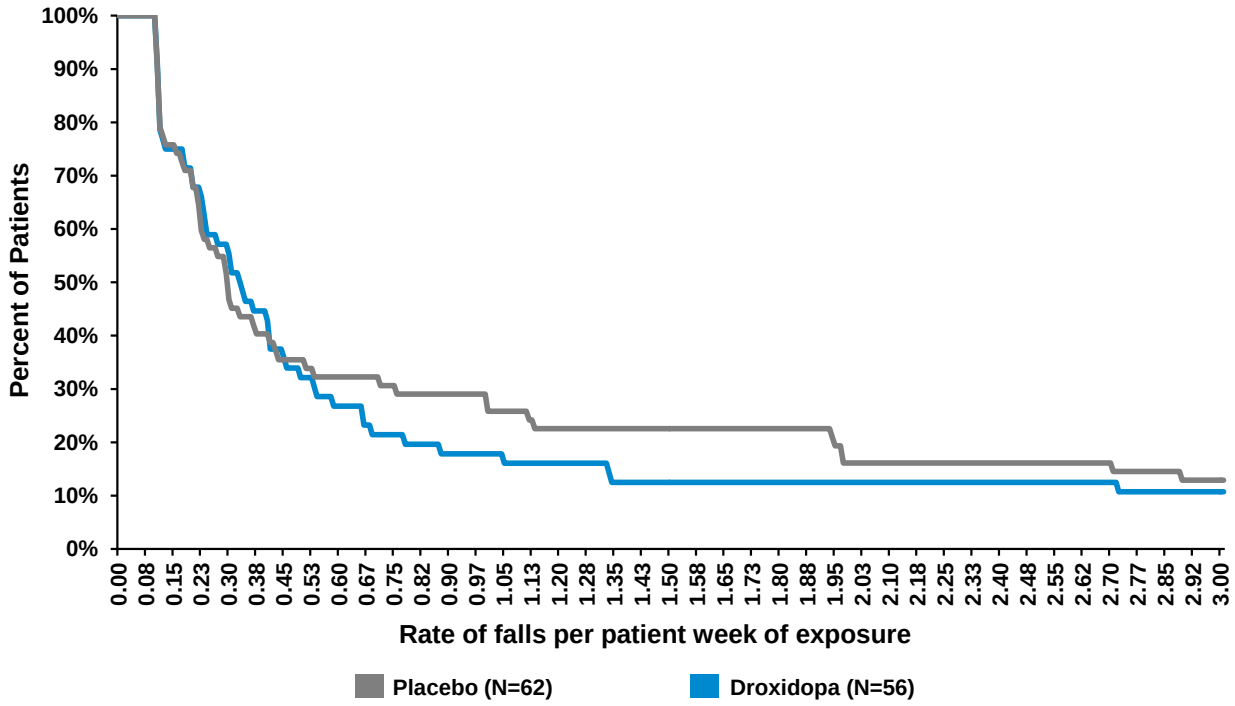


MDE=missing data excluded.

Notes: All subjects had evaluable records defined as any non-missing response in the daily falls diary. Patient rate of falls is calculated for each patient as the (total number of falls/number of evaluable days)*7. Number of falls by each week is cumulative; i.e., a patient who fell during Week 1 also fell by Week 2.

A cumulative distribution curve demonstrating the rate of falls per week in patients with ≥1 fall is presented in Figure 6-30. In this figure, a shift down or to the left represents a decrease in the percentage of patients with a higher rate of falls (i.e., a reduction in the rate of falls). The shift shows a wide distribution of patients treated with droxidopa experience benefits on falls compared with placebo.

Figure 6-30 Study 306B+Interim Analysis Dataset: Cumulative Distribution Curve for Rate of Falls



ITT=Intent-to-Treat.
Notes: Patients are included in a treatment arm according to how they were randomized. The data includes all patients who reported a fall during the study.

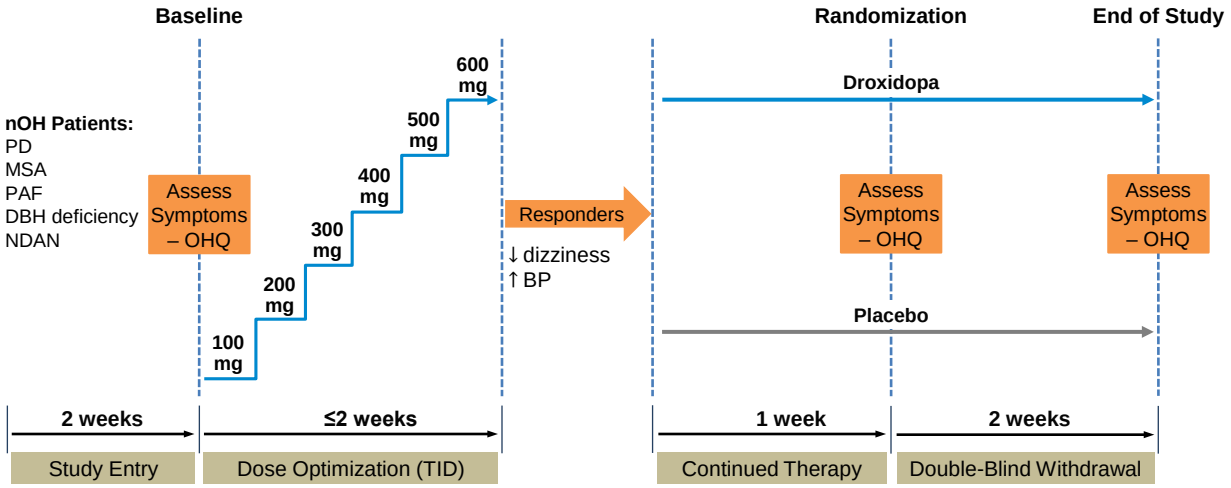
6.1.4 Study 302

While Study 302 is a supportive Phase 3 study with consistent trends favoring droxidopa on multiple symptomatic endpoints, it was a smaller study (N=101) with a different design compared with Study 301 and Study 306B. Study 302 was a Phase 3, multi-center, multi-national, double-blind, randomized-withdrawal, placebo-controlled, parallel-group study that included an initial open-label dose titration period, a 7-day open-label treatment period, and a 14-day randomized-withdrawal period in which patients were treated with either their individually optimized dose of droxidopa or matching placebo (see Appendix 2; Section 10.2.3 for further study design details). Similar to Study 301, Study 302 was conducted in patients with symptomatic nOH associated with PD, MSA, PAF, DBH Deficiency, or NDAN. Inclusion and exclusion criteria were similar to those for Study 301 (Table 6-1).

The primary efficacy endpoint was the mean change in dizziness/lightheadedness (the OHSA Item 1 score) from Randomization to End of Study. Based on overall 0.05 two-sided significance level, the study had greater than 80% power to detect a difference of 1.6 in the OHSA Item 1 score (primary variable) with 42 evaluable patients in each randomized treatment group in a 1:1 ratio (i.e., 84 patients in total).

The design of Study 302 is presented graphically in Figure 6-31 (see Appendix 2; Table 10-4 for a tabular summary of study results). As part of the study design, all patients entered an open-label, dose titration/optimization period, where they were titrated to effect. Details regarding the dose titration period in Study 302 are similar to those described for Study 301 in Section 6.1.1.

Figure 6-31 Study 302: Study Design



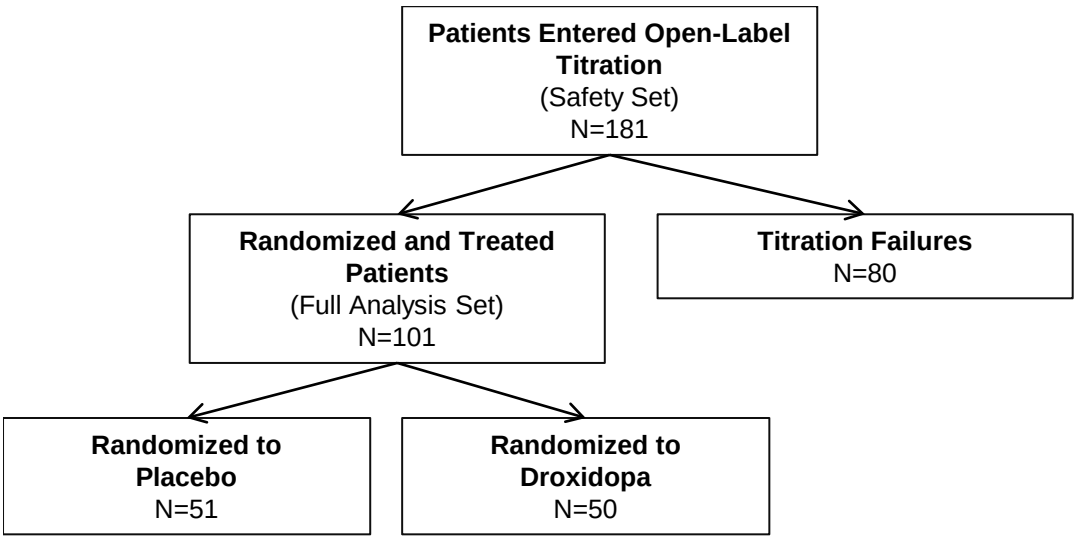
DBH=dopamine beta hydroxylase; MSA=Multiple System Atrophy; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; OHQ=Orthostatic Hypotension Questionnaire; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; TID=three times daily.

6.1.4.1 Disposition, Demographics, and Concomitant Medications

6.1.4.1.1 Disposition

Of the reported 266 patients screened, 181 eligible patients entered the open-label dose-titration period; the remaining 85 patients were screen failures. Of the 181 patients who entered the dose-titration period, 101 were randomized into the double-blind phase of the study (placebo: 51 patients; droxidopa: 50 patients) and comprise the FAS (Figure 6-32).

Figure 6-32 Study 302: Patient Disposition



Based on a *post-hoc* evaluation, of the 80 patients treated with droxidopa only during the open-label titration phase (i.e., patients who were classified as titration failures and did not receive double-blind study drug), the most common reason for discontinuation was reaching the maximum dose without meeting the response criteria (24 [30.0%] patients), followed by AEs (22 [27.5%] patients), BP elevation (21 [26.3%] patients), and other (13 [16.3%] patients).

6.1.4.1.2 Demographics

Demographic characteristics were similar to Study 301 and similar between the droxidopa and placebo treatment groups in Study 302 (Table 6-12).

Table 6-12 Study 302: Summary of Demographic and Baseline Characteristics (FAS)

	RCT Phase	
	Placebo (N=51)	**Droxidopa (N=50)**
Sex [n (%)]		
Male	32 (62.7)	30 (60.0)
Female	19 (37.3)	20 (40.0)
Race [n (%)]		
White	48 (94.1)	49 (98.0)
Asian	1 (2.0)	1 (2.0)
American Indian/Alaskan Native	1 (2.0)	0
Hispanic/Latino	1 (2.0)	0
Primary Clinical Diagnosis [n (%)]		
Parkinson's Disease	23 (45.1)	21 (42.0)
Multiple System Atrophy	13 (25.5)	17 (34.0)
Pure Autonomic Failure	10 (19.6)	8 (16.0)
Dopamine Beta Hydroxylase Deficiency	1 (2.0)	0
Non-Diabetic Neuropathy	3 (5.9)	2 (4.0)
Other Diagnosis	1 (2.0)	2 (4.0)
Age (Years) at Screening		
Mean (SD)	66.6 (11.25)	63.1 (13.76)
Min, Max	40, 88	24, 88
Geographic Region [n (%)]		
US	32 (62.7)	25 (50.0)
Non-US	19 (37.3)	25 (50.0)
Disease Severity		
Mean Baseline Dizziness, n	51	50
Mean (range)	6.3 (2,10)	6.6 (3,10)
Baseline SBP upon Standing +3 Minutes (mmHg), n	50	50
Mean (SD)	88.0 (19.04)	87.0 (17.60)

FAS=Full Analysis Set; Max=maximum; Min=minimum; RCT=Randomized-Controlled Treatment; SD=standard deviation; US=United States.

6.1.4.1.3 Concomitant Medications

Similar to Study 301, concomitant medication use was typical of the patient population and was similar between the droxidopa and placebo groups. The majority of patients in Study 302 took concomitant medications. Patients were instructed not to change their concomitant medication use during the study.

Of those patients randomized to double-blind treatment, 50 (98.0%) placebo-treated and 48 (96.0%) droxidopa-treated patients took concomitant medications. DOPA and DOPA derivatives were the most common concomitant medications by ATC class and their use was comparable between placebo-treated (56.9%) and droxidopa-treated patients (54.0%).

Mineralocorticoids were used by 25.5% of placebo-treated and 32.0% of droxidopa-treated patients. Overall, concomitant medication use was typical of this patient population.

6.1.4.2 Dizziness (OHSA Item 1) and OHQ Composite Score

In Study 302, a randomized-withdrawal study, patients on placebo were expected to worsen following randomization, and thereby have higher OHQ scores.

At End of Study, placebo-treated patients had a mean increase (i.e., worsening) from Randomization of 1.9 units in their OHSA Item 1 score compared with a 1.3 unit increase in droxidopa-treated patients, resulting in a 0.6 unit treatment difference favoring droxidopa, a difference that was not statistically significant (p=0.509; Table 6-13 and Figure 6-33). The absence of a statistically significant treatment effect may be potentially due to a carry-over effect in this randomized-withdrawal study (see Section 6.2.1.2.2 for a discussion of carry-over effects).

However, a *post-hoc* analysis revealed that treatment with droxidopa resulted in a larger improvement in the mean change from Randomization to End of Study in the OHQ composite score (treatment difference of 1.11; p=0.026; Table 6-13 and Figure 6-33), a result that is consistent with Study 301.

Table 6-13 Study 302: Dizziness (OHSA Item 1) and OHQ Composite Scores (FAS)

	Placebo (N=51)		Droxidopa (N=50)			
	n	Δ Mean (SD)	n	Δ Mean (SD)	Treatment Difference	p-value
Primary Efficacy Endpoint						
OHSA Item 1 (dizziness/lightheadedness)[1]	51	1.9 (3.16)	50	1.3 (2.75)	0.6	0.509[3]
***Post-hoc* Analysis**						
OHQ Composite Score[2]	49	1.22 (2.39)	47	0.11 (2.18)	1.11	0.026[4]

Δ=Change; LOCF=last observation carried forward; MDE=missing data excluded; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SBP=systolic blood pressure; SD=standard deviation.

Note: Efficacy endpoints are presented in hierarchical order.

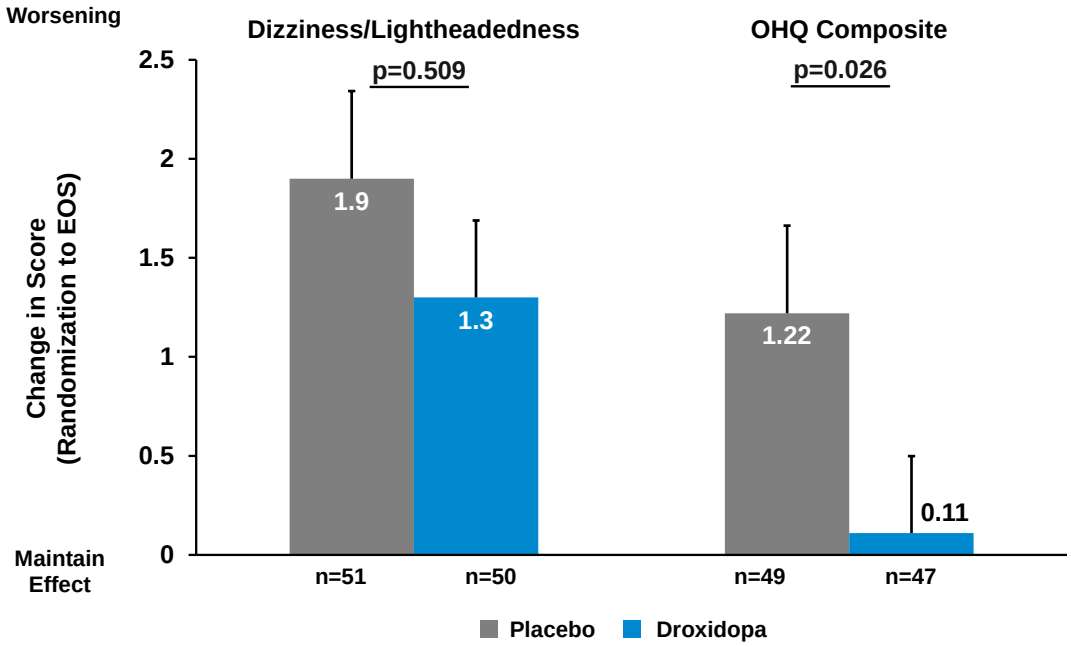
1 Data analyzed using LOCF.

2 Data analyzed with MDE.

3 The change from Randomization was evaluated using the Wilcoxon rank-sum test.

4 The change from Randomization to End of Study was evaluated using the Wilcoxon rank-sum test conducted with as a *post-hoc* analysis.

Figure 6-33 Study 302: Dizziness (OHSA Item 1) and OHQ Composite Score (FAS)



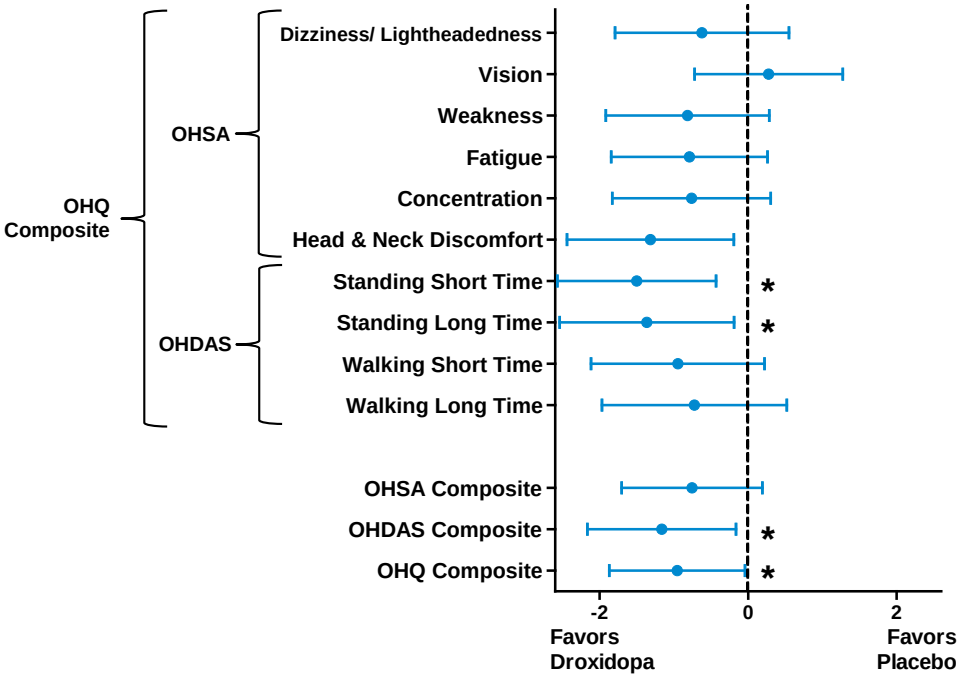
EOS=End of Study; FAS=Full Analysis Set; LOCF=last observation carried forward; MDE=missing data excluded; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: OHSA Item 1 data analyzed using LOCF. OHQ data analyzed with MDE.

Note: The OHSA Item 1 change from Randomization was evaluated using the Wilcoxon rank-sum test. The OHQ composite score change from Randomization to End of Study was evaluated using two-sided Wilcoxon rank-sum tests conducted with a post-hoc analysis.

In Study 302, droxidopa-treated patients experienced benefits across a broad range of other symptoms as well as the impact of these symptoms on their ability to perform activities of daily living (Figure 6-34). Droxidopa-treated patients showed consistent, numerical improvements versus placebo on 9 of the 10 individual items of the OHQ. These consistent improvements observed across the individual items within the OHQ, in addition to the OHQ composite score, demonstrate a broad benefit for droxidopa.

Figure 6-34 Study 302: Treatment Differences for OHQ Components (FAS, LOCF)



FAS=Full Analysis Set; LOCF=last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using a Wilcoxon rank-sum test (*p<0.05). Confidence intervals are not adjusted for covariates and may cross the zero line despite statistical significance.

6.1.4.3 Clinical Global Impressions of Severity and Improvement

In Study 302, at End of Study, there was a statistically significant (p=0.008) benefit favoring droxidopa on the patient-reported CGI-S and a strong trend favoring droxidopa on the clinician-reported CGI-S (p=0.052) (Appendix 9; Table 10-13).

Although both the clinician- and patient-reported CGI-I at End of Study failed to show statistically significant differences between droxidopa and placebo, numerical improvements in favor of droxidopa were observed for both the clinician- and patient-reported CGI-I (Appendix 9; Table 10-14).

6.1.4.4 Efficacy Conclusions from Study 302

Although Study 302 failed to meet its primary endpoint, *post-hoc* analyses and secondary endpoints provide supportive evidence consistent with the results from Study 301 and Study 306B demonstrating that droxidopa provides meaningful symptomatic improvement for patients with nOH.

6.1.5 Other Studies Evaluating Blood Pressure

A pharmacological effect on BP is not considered an acceptable surrogate efficacy endpoint by the FDA. However, BP change is an important hemodynamic marker. Therefore, evidence of an increase in standing SBP can support symptomatic endpoints demonstrating effectiveness.

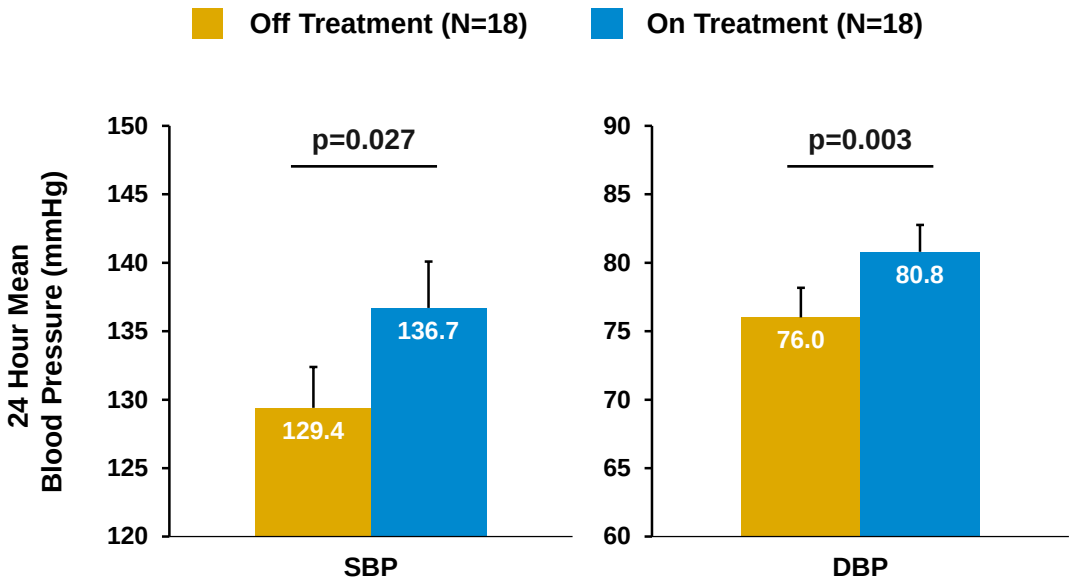
Studies 301, 306, 302, and 303 were not optimally designed to precisely characterize droxidopa's effect on BP. Blood pressure was recorded as a single point in time at study visits during a recommended window surrounding measurement timing post-droxidopa dose.

The smaller, supportive Chelsea-sponsored studies, Studies 101, 102, and 305 (see Appendix 2; Section 10.2 for study design details) were designed with rigorous BP monitoring to assess the effect of droxidopa on BP. The BP results from these supportive trials are summarized below.

Study 305

Study 305 (N=18) was designed to evaluate the impact of droxidopa treatment on nOH patients' average 24-hour ambulatory BP. As shown in Figure 6-35, there was a statistically significant increase of 7.3 mmHg (±11.72) in the 24-hour mean SBP (p=0.027) in subjects comparing their off- vs. on-drug treatment periods and similar statistically significant increases were observed for DBP (p=0.003).

Figure 6-35 Study 305: 24-hour Mean Standing Blood Pressures Off- and On-Treatment

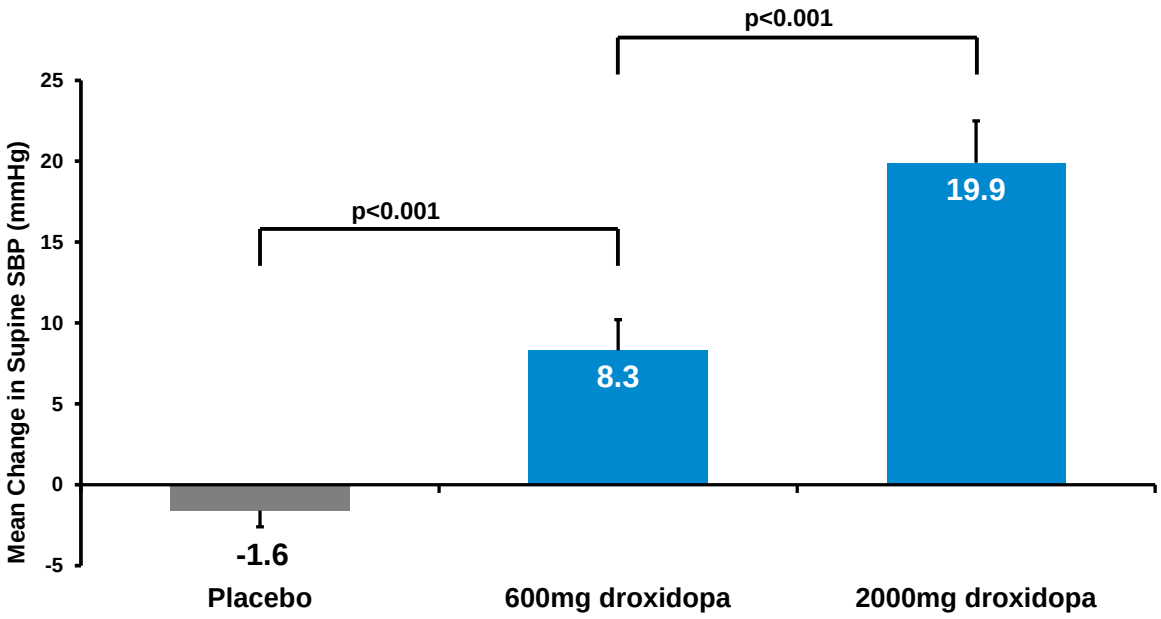


DBP=diastolic blood pressure; SBP=systolic blood pressure.
Note: The p-value is based on Wilcoxon signed rank test comparing off-treatment vs. on-treatment SBP.

Study 102

Study 102, a dedicated QTc study of 52 healthy volunteers, was a randomized, double-blind, single-site, 4-period crossover study to determine whether droxidopa administered as a single therapeutic (600 mg) and a single supratherapeutic (2000 mg) dose delays cardiac repolarization. As shown in Figure 6-36, there was a dose-dependent statistically significant increase in supine SBP in subjects taking droxidopa 600 and 2000 mg compared with placebo.

Figure 6-36 Study 102: Supine Systolic Blood Pressures (3 Hours Post-dose)

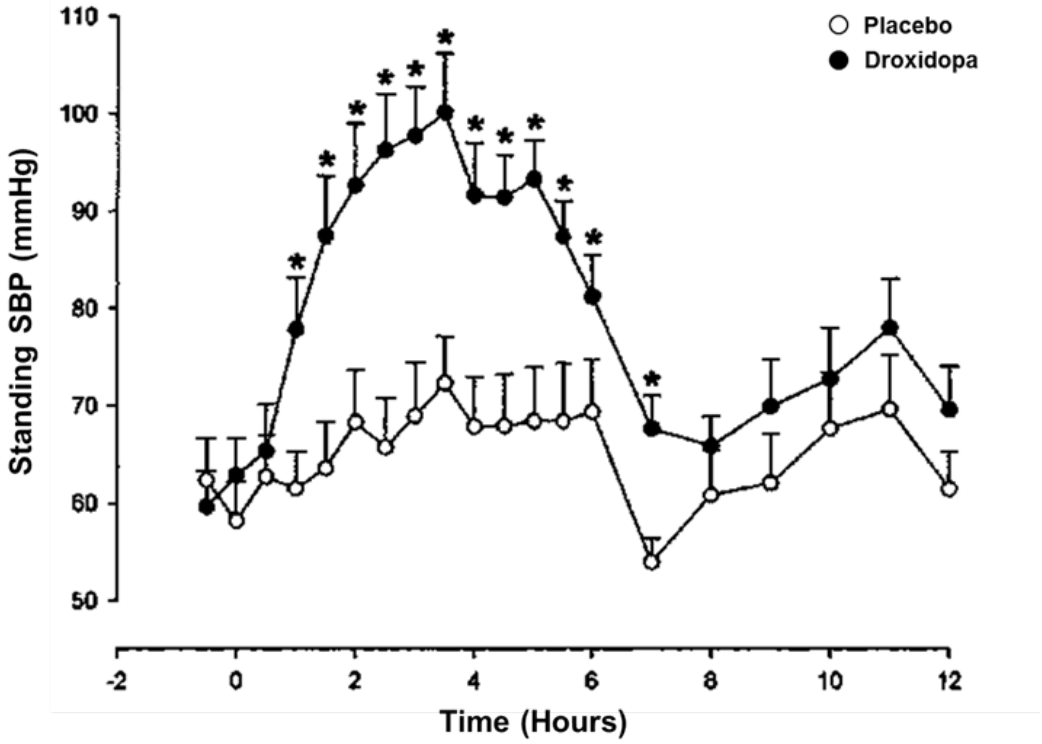


ANOVA=analysis of variance; SBP=systolic blood pressure.
Note: The change in SBP was measured 3 hours following single droxidopa dose, and healthy volunteers (N=52) were semi-recumbent. Data were analyzed using ANOVA followed by Tukey tests of pairwise significance.

Kaufmann et al, 2003

A double-blind crossover study in MSA and PAF patients study performed by Kaufmann et al, 2003 evaluated whether droxidopa (in doses ranging from 200 to 2000 mg) could raise BP. As shown in Figure 6-37, administration of droxidopa increased standing BP in all patients both after standing for 3 minutes compared with placebo ($p<0.05$).

Figure 6-37 Standing Blood Pressures (Kaufmann, et al 2003), N=19

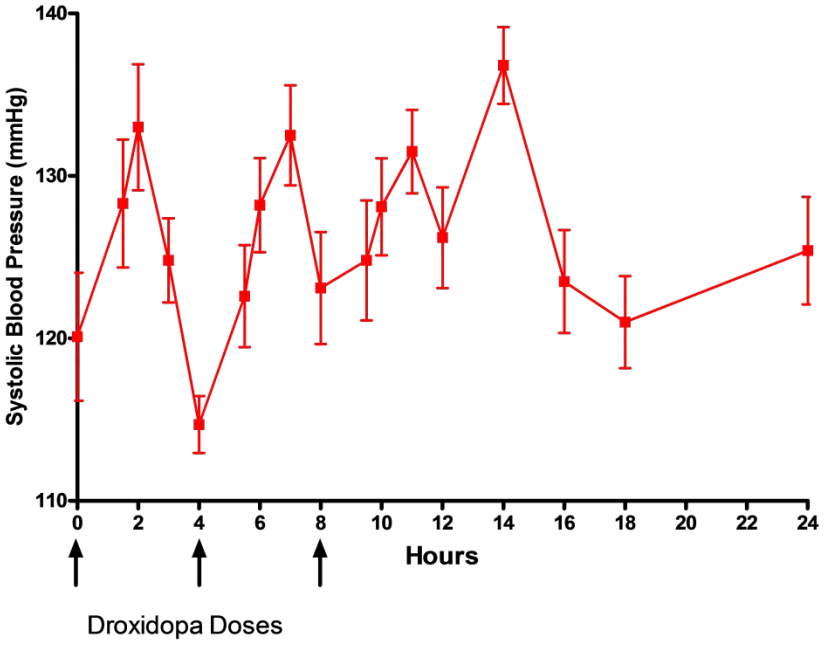


ANOVA=analysis of covariance; SBP=systolic blood pressure.
Note: * indicates $p<0.05$; the results were analyzed with a 2-factor ANOVA with repeated measures.

Study 101

Study 101 was a two-part food-effect/BE/PK study. Part II of the study was an open-label design; all subjects received 3 doses of 300 mg droxidopa (three 100 mg capsules/dose) at 4-hour intervals and were followed for a 24-hour period to evaluate the PK profile of droxidopa 300 mg TID. As shown in Figure 6-38, SBP increased after droxidopa administration and peaked at 2 to 3 hours post-dose.

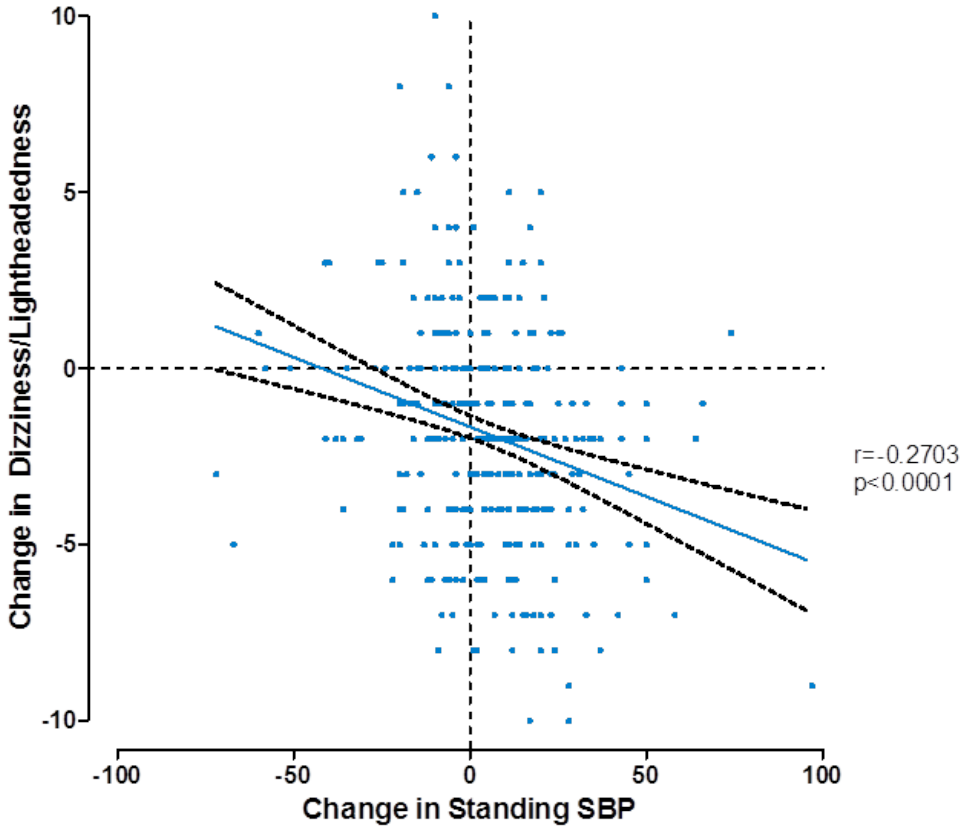
Figure 6-38 Study 101: Systolic Blood Pressures



Studies 301 and 306 Correlation Analysis

In addition to these studies designed with rigorous BP monitoring, Studies 301 and 306 evaluated BP and used the OHSA to evaluate dizziness/lightheadedness in the same patients. As shown in Figure 6-39, there was a weak but statistically significant correlation ($r=-0.2703$, $p<0.0001$) between an increase in standing SBP and improvements in dizziness/lightheadedness in Studies 301 and 306.

Figure 6-39 Study 306 and Study 301: Correlation between Blood Pressure and Dizziness/Lightheadedness Symptoms



SBP=systolic blood pressure
Note: The results were analyzed by non-parametric Spearman correlation and linear regression.

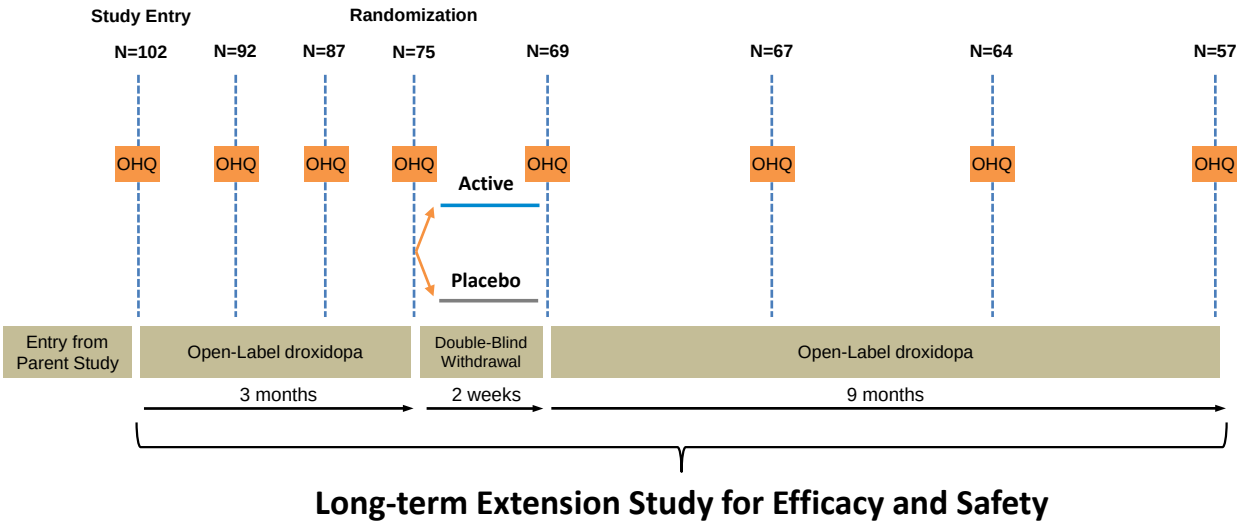
Taken together, the results of these studies clearly show that droxidopa has a pharmacodynamic effect consistent with treatment benefits in symptomatic nOH.

6.2 Long-Term Efficacy Studies: Durability of Effect

6.2.1 Study 303

Study 303 was a Phase 3, multi-center, multi-national, open-label, long-term extension study to evaluate the long-term safety and efficacy of droxidopa in patients with nOH (Figure 6-40). The study had an initial 12-week open-label period, followed by 2 weeks of treatment with droxidopa or placebo in a double-blind, randomized-withdrawal period, and then an open-label long-term extension period in which patients were again treated with their individualized dose of droxidopa for up to 1 year (US patients could continue beyond the 1 year duration; see Appendix 2; Section 10.2.4 for further study details).

Figure 6-40 Study 303: Study Design



OHQ=Orthostatic Hypotension Questionnaire.
Note: Ns in the figure represent the Safety Set for each time point.

Study 303 was originally intended as an open-label safety extension study for patients from Studies 301 and 302. Based on FDA guidance, a 2-week double-blind, withdrawal period was included in the trial in order to provide some additional information on the durable effects of droxidopa. Ultimately, 75 patients participated in the randomized-withdrawal portion of the study.

Efficacy results from the 2-week randomized-withdrawal period of the study as well as the 3 months of open-label droxidopa treatment prior to the randomized-withdrawal period are discussed in Section 6.2.1.2; the overall long-term open-label efficacy results (i.e., out to 12 months of treatment) are provided in Section 6.2.1.3. Of note, Study 303 was not powered to show a statistical difference between treatment groups in the randomized-withdrawal period of the study.

6.2.1.1 Disposition, Demographics, and Concomitant Medications

6.2.1.1.1 Disposition

A total of 103 patients enrolled in Study 303 and 102 received at least 1 dose of study drug. The majority of these patients had been previously enrolled in Study 302. Of the 103 patients enrolled, 79 patients (76.7%) completed the 3-month open-label period of the study, 75 (72.8%) were randomized into the 2-week, double-blind, randomized-withdrawal portion of the study (69 of whom completed this portion of the study), and 54 (52.4%) patients completed the entire study per protocol (12 months of treatment).

6.2.1.1.2 Demographics

In Study 303, most patients enrolled in the study had a primary clinical diagnosis of PD (47.1%), MSA (26.5%), or PAF (17.6%). Overall, the mean age of patients was 66 years (range: 30-88 years). The majority of patients were male (59.8%) and patients were predominantly White (97.1%).

6.2.1.1.3 Concomitant Medications

The pattern of concomitant medication use in Study 303 was similar to that presented above for Studies 301 and 302 (Section 6.1.1.1 and Section 6.1.4.1, respectively). In the 3-month open-label period, 98.0% of patients took concomitant medications; in the double-blind randomized-withdrawal period, 94.6% of placebo-treated and all (100%) of the droxidopa-treated patients took concomitant medications; and in the long-term follow-up period (i.e., the 9-month open-label period following the 2-week randomized-withdrawal period), all (100.0%) of the patients took concomitant medications. DOPA and DOPA derivatives were the most common concomitant medications by ATC class and their use was comparable between patients participating in the 3-month open-label period (59.8%); in placebo-treated (56.8%) and droxidopa-treated patients (60.5%) in the double-blind randomized-withdrawal period; and in the long-term follow-up period (59.5%). Sinemet (carbidopa/levodopa) was the most commonly used DOPA derivative, taken by 42.2% of patients in the 3-month open-label period; 43.2% of placebo-treated and 39.5% of droxidopa-treated patients in the double-blind randomized-withdrawal period; and 45.9% of patients in the long-term follow-up period.

6.2.1.2 Study 303 Randomized-Withdrawal Period

The prospectively-defined endpoint was the mean change from Randomization to the end of the 2-week randomized withdrawal period of the OHQ composite score following the completion of 3 months of treatment with open-label droxidopa.

6.2.1.2.1 OHQ Composite and Dizziness (OHSA Item 1) Scores

Although treatment differences were in favor of droxidopa, statistically significant reductions in the mean change from Randomization in the OHQ composite score as well as OHSA Item 1 (Table 6-14) were not observed in the randomized-withdrawal period of Study 303. Of note, Study 303 was not powered to show a statistical difference between treatment groups in the randomized-withdrawal period of the study.

Table 6-14 Study 303: Change in OHQ Composite Score and OHSA Item 1 from Randomization to End of the Randomized-Withdrawal Period (FAS, LOCF)

	Placebo (N=37)		Droxidopa (N=38)		
Efficacy Endpoints	**n**	**Δ Mean (SD)**	**n**	**Δ Mean (SD)**	**p-value[1]**
Primary Efficacy Endpoint					
OHQ Composite Score	37	0.90 (1.550)	37	0.57 (1.891)	0.438
Secondary Efficacy Endpoint					
OHSA Item 1 Score	37	1.3 (2.21)	38	0.9 (2.39)	0.251

Δ=change; ANCOVA=analysis of covariance; FAS=Full Analysis Set; LOCF=last observation carried forward; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SD=standard deviation.

1 The difference between placebo and droxidopa with respect to changes from Baseline and Randomization were evaluated using a non-parametric ANCOVA model using Cochran-Mantel-Haenszel methodology based on rank statistics adjusted for the Randomization value as a covariate.

Note that in Study 303, all patients were taking droxidopa during the 12-week open-label period prior to Randomization. Reductions (improvements) in the OHQ composite score from Baseline to Randomization were observed in both patients who were subsequently randomized to placebo (mean change of -3.35 units) and patients subsequently randomized to droxidopa (mean change of -3.13 units). Similarly, reductions (improvements) in OHSA Item 1 from Baseline to Randomization were observed in both patients who were subsequently randomized to placebo (mean change of -4.1 units) and patients subsequently randomized to droxidopa (mean change of -3.9 units).

At the end of the randomized-withdrawal period, the placebo-treated patients failed to return to Baseline, suggesting that a carry-over effect (similar to that observed in Study 302) may have confounded the results of this portion of the study (a discussion of carry-over effects is presented in Section 6.2.1.2.2).

6.2.1.2.2 Blood Pressure and a Discussion of a Carry-Over Effect

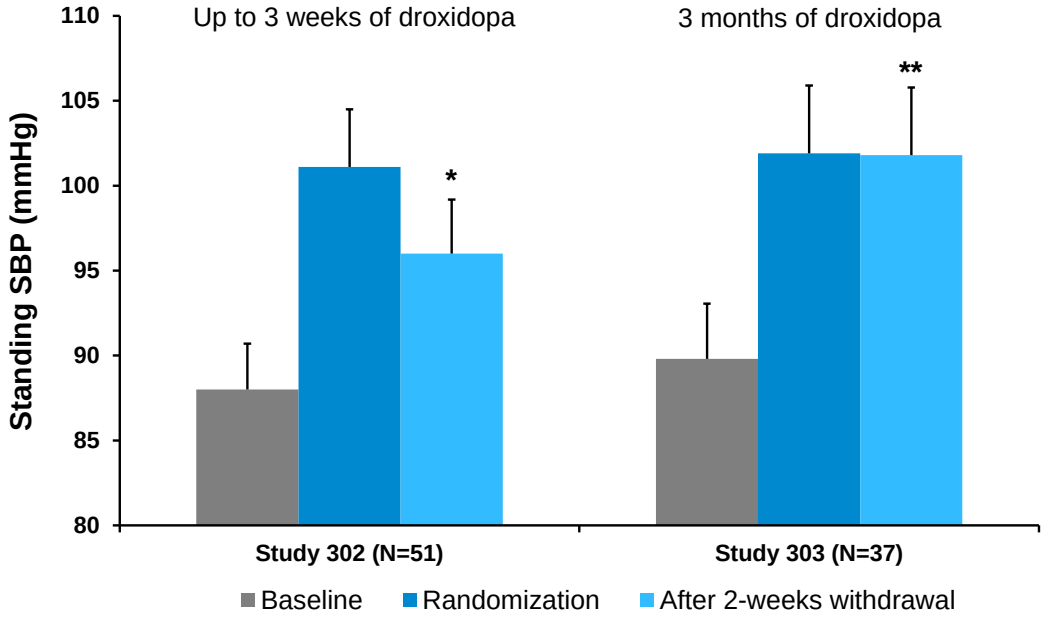
While Studies 302 and 303 were withdrawal designs theoretically enriched to show clinical benefit, these studies could have been confounded in their ability to detect a treatment effect by a failure to effectively enrich or due to the presence of a carry-over effect.

Carry-over effects are sustained symptomatic and BP improvements relative to Baseline following treatment with droxidopa in patients following discontinuation of therapy. Patients withdrawn from droxidopa in Studies 302 and 303 (during the double-blind, randomized-withdrawal period of the studies) continued to experience increases in SBP (Figure 6-41). In both studies, patients' mean SBP increased from Baseline to approximately 90 mmHg to above 100 mmHg after continuous droxidopa therapy (up to 3 weeks in Study 302 and 3 months in Study 303). After 2 weeks of placebo treatment, mean SBP did not return to Baseline despite the 2- to 3-hour serum half-life of droxidopa. These differences in BP values

compared with Baseline were statistically significant. Similar observations were noted for clinical symptoms.

These data suggest that, similar to levodopa, droxidopa may continue to provide benefits to patients after it has been withdrawn.

Figure 6-41 After Withdrawal of Droxidopa: Pressor Effect is Maintained



* p=0.011 compared to baseline
** p<0.001 compared to baseline

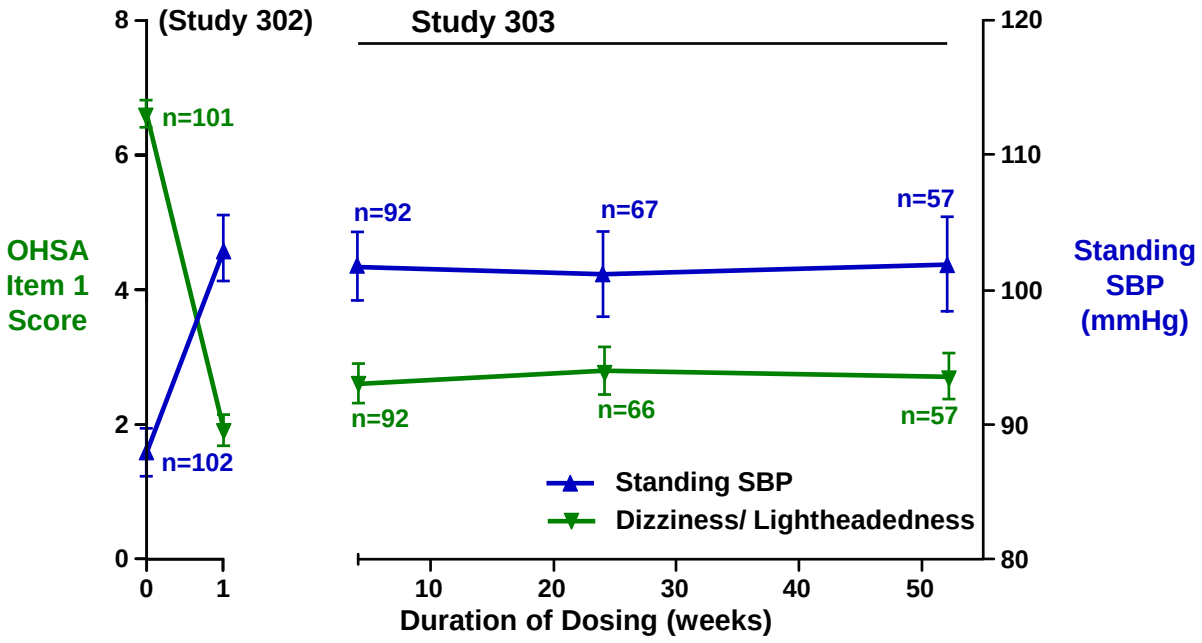
SBP=Systolic blood pressure
Note: Data shown are only for patients randomized to placebo. Change from Baseline was analyzed using Wilcoxon signed rank test.
Note: Values at Randomization for Study 302 were obtained after up to 2 weeks of open-label titration with droxidopa followed by 1 week of open-label treatment with droxidopa. Values at Randomization for Study 303 were obtained after 3 months of open-label treatment with droxidopa.

6.2.1.3 Study 303 Long-Term Extension

In addition to the primary endpoint (Section 6.2.1.2), OHSA Item 1 and BP changes were assessed during the entire open-label period of the study was well as at the end of the 2-week randomized-withdrawal portion of the study and were pre-specified efficacy endpoints.

Results based on the long-term open-label data from Study 303 provide strong evidence of a durable treatment effect with droxidopa. As demonstrated in Figure 6-42, decreases in the OHSA Item 1 score and increases standing SBP were consistent and durable with long-term droxidopa treatment in Study 303; changes observed at Week 1 in both the OHSA Item 1 score and standing SBP were consistently maintained out to Week 52. Similar results (data not shown) were observed for the individual items of the OHQ as well as clinician- and patient-reported assessments of the CGI-S and CGI-I.

Figure 6-42 Study 303: Summary of OHSA Item 1 Score and Standing SBP Over Time (Safety Set[1] and FAS[2], MDE)



FAS=Full Analysis Set; MDE=missing data excluded; OHSA=Orthostatic Hypotension Symptom Assessment; SBP=systolic blood pressure.

Note: Baseline was the last non-missing value prior to the first dose of study drug as part of Study 301 or 302.

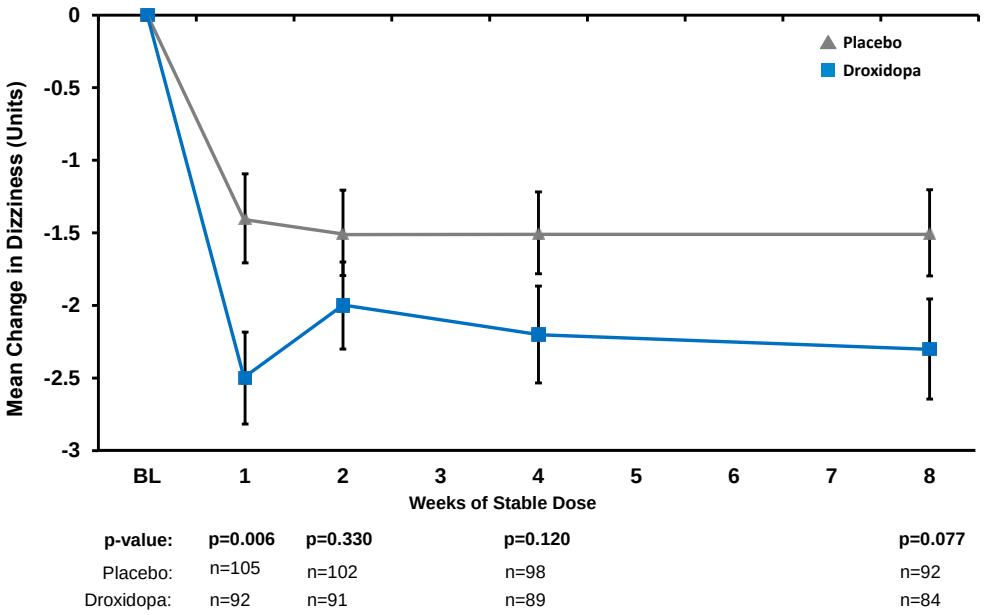
1 The Safety Set (MDE), which included all patients who received at least 1 dose of study drug, including those who were not randomized into the 2-week double-blind randomized-withdrawal portion of the study, was utilized to assess the long-term efficacy of all patients administered open-label droxidopa in the first 3 months.

2 The Full Analysis Set (MDE) was used for time points beyond 3 months.

6.2.2 Overall Study 306: Week 8

Although data from Study 306B did not show statistically significant durable benefits for droxidopa at Week 8 on the mean change from Baseline in OHSA Item 1 (p=0.187), data from the combined Study 306B+Interim Dataset showed trends for improvement as measured by the mean change from Baseline to Week 8 in OHSA Item 1 (p=0.077, Figure 6-43).

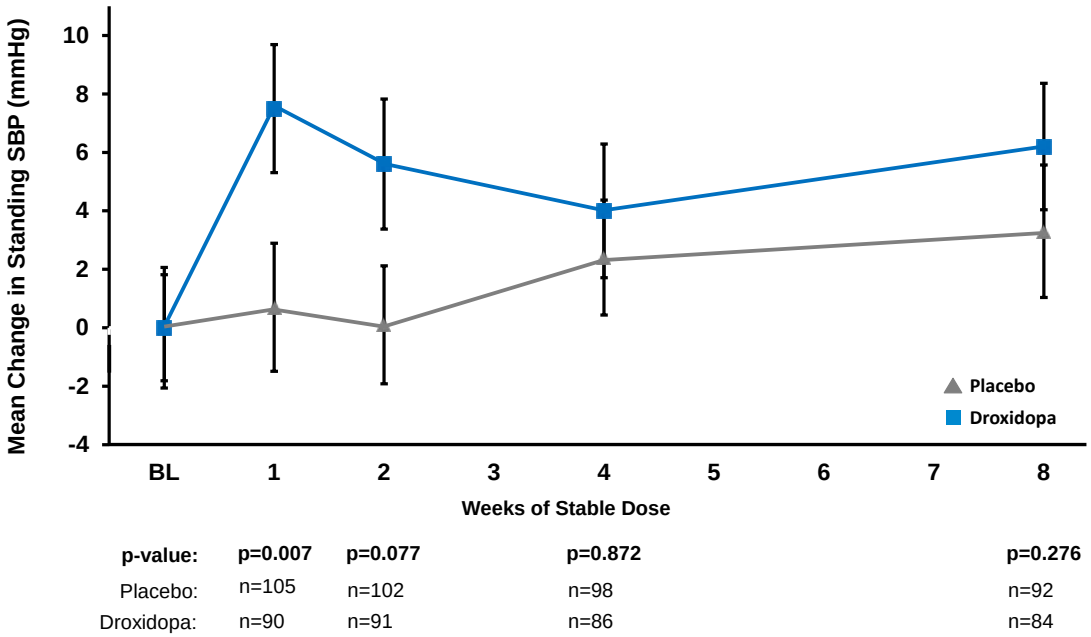
Figure 6-43 Study 306B+Interim Analysis Dataset: Dizziness (OHSA Item 1) Means Over Time (FAS, MDE)



ANCOVA=analysis of covariance; BL=Baseline; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: Treatment difference for pooled studies tested using a parametric ANCOVA model with effects for treatment, Baseline value, and study.

With respect to lowest standing SBP during the OST, patients in the droxidopa group experienced greater increases from Baseline at each study visit compared with the placebo group. Across all study visits, mean increases from Baseline in lowest standing SBP ranged from 4.0 mmHg to 7.5 mmHg in the droxidopa group compared with a range of 0.1 mmHg to 3.3 mmHg in the placebo group (Figure 6-44).

Figure 6-44 Study 306B+Interim Analysis Dataset: Mean Change in Lowest Standing Systolic Blood Pressure



p-value:	p=0.007	p=0.077	p=0.872	p=0.276
Placebo:	n=105	n=102	n=98	n=92
Droxidopa:	n=90	n=91	n=86	n=84

ANCOVA=analysis of covariance; BL=Baseline; SBP=systolic blood pressure.
Note: Treatment difference for pooled studies tested using a parametric ANCOVA model with effects for treatment, Baseline value, and study.

6.2.3 Conclusions on Durability of Effect

While Chelsea has not confirmed a long-term clinical benefit for droxidopa, there are numerous data supporting durable benefits.

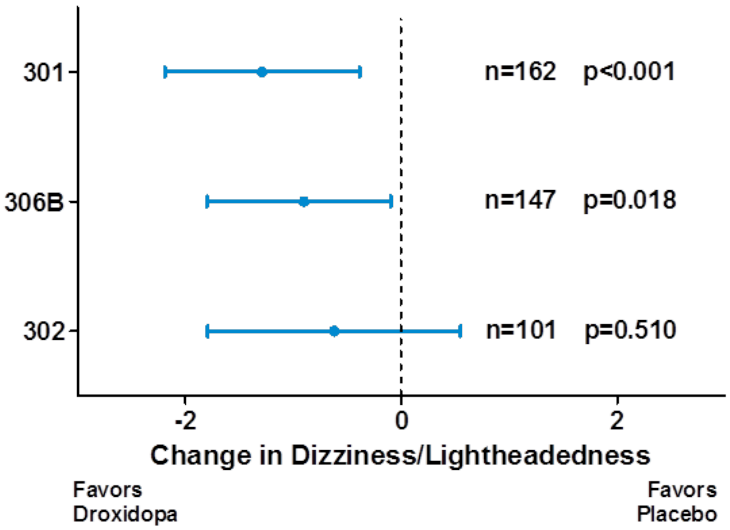
Results from long-term studies (Study 303 following up to 12 months of open-label treatment and Study 306 following up to 2 months of double-blind treatment) suggest that the benefits of droxidopa on both symptoms (i.e., OHSA Item 1) and standing BP are durable. Evidence of the durability of the effect of droxidopa has been previously demonstrated and reported in the literature. The effects of droxidopa on alpha 2-adrenergic receptors in platelet membranes were investigated in a patient with FAP, 2 patients with MSA, and 2 patients with PD. Each patient was treated for at least 6 months (Azuma et al, 1991). While droxidopa alone, or in combination with decarboxylase inhibitor benserazide hydrochloride, produced sustained increase in plasma NE and clinical improvement, it did not induce a change in the number of alpha 2-adrenergic receptors in platelet membranes. A study conducted by Azuma et al, 1988, in a patient with FAP showed no change in the pressor response to infused NE and isoproterenol after 5 weeks of droxidopa treatment. Finally, in a study conducted by Ushiyama et al, 1996, in a single patient with acute pandysautonomia, it was demonstrated that the pressor response to droxidopa was unchanged after 31 months of treatment.

To further characterize the effect of droxidopa, the Sponsor has initiated a large 450 patient randomized, placebo-controlled trial (intended as a post-marketing study) with a 3-month treatment period. Topline data from this study are expected in late 2016. The proposed post-marketing study design is discussed in Section 6.4.

6.3 Summary of Efficacy

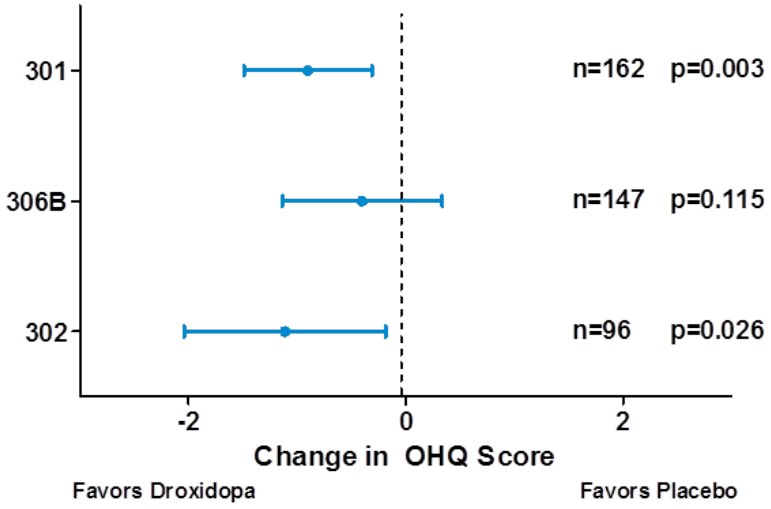
The overall data from 2 adequate and well-controlled, multi-center, double-blind, randomized induction design studies (Studies 301 and 306B) demonstrate that droxidopa provides clear and consistent short-term benefits for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN. These data are supported by secondary data from an additional randomized, double-blind, placebo-controlled withdrawal study (Study 302). Each of the 3 studies had limitations (Study 301 was affected by site effects; Study 306B had a disproportionately higher number of dropouts during titration in patients randomized to droxidopa compared with placebo; and Study 302 failed on the primary endpoint and was impacted by a possible carry-over effect). Nonetheless, short-term effectiveness was demonstrated across a range of symptoms and pharmacodynamic measures including improvements in dizziness/lightheadedness/syncopal symptoms, the cardinal symptom of nOH (Figure 6-45); the overall OHQ composite score (Figure 6-46); increases in standing BP (Figure 6-47); and global improvements as assessed by clinicians (CGI-S and CGI-I). There was also a strong suggestion of a reduction in falls and fall-related injuries (Study 306B).

Figure 6-45 Treatment Differences for Dizziness/Lightheadedness Symptoms Across Studies 301, 306B, and 302



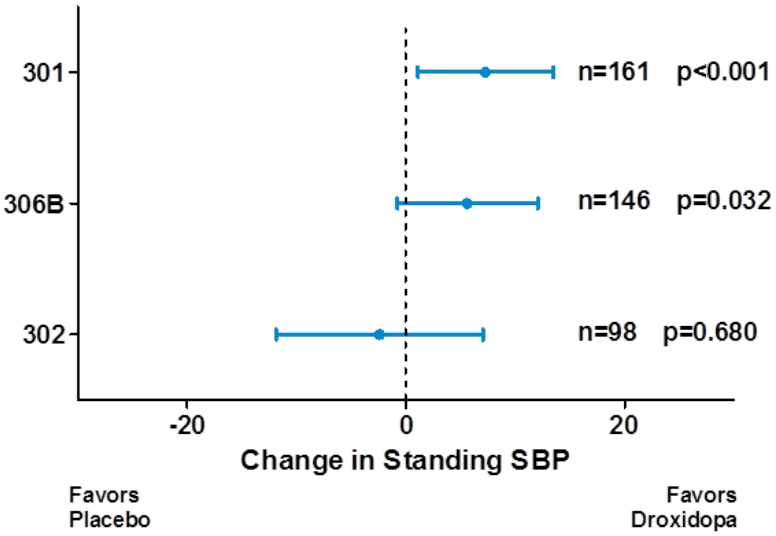
ANCOVA=analysis of covariance; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using either a non-parametric ANCOVA model including a factor for randomized treatment along with the value at Randomization as a covariate (Studies 301 and 306B) or a Wilcoxon Rank Sum test (Study 302).

Figure 6-46 Treatment Differences for OHQ Composite Score Across Studies Across Studies 301, 306B, and 302



ANCOVA=analysis of covariance; OHQ=Orthostatic Hypotension Questionnaire.
Note: The differences between placebo and droxidopa with respect to changes were evaluated using an ANCOVA model including a factor for randomized treatment along with the OHQ at Randomization/Baseline as a covariate (Studies 301 and 306B) or a Wilcoxon Rank Sum test (Study 302). Confidence intervals are not adjusted for covariates and may cross the zero line despite statistical significance.

Figure 6-47 Treatment Differences for Change in Standing SBP Across Studies 301, 306B, and 302



ANCOVA=analysis of covariance; SBP=systolic blood pressure.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using either a non-parametric ANCOVA model including a factor for randomized treatment along with the value at Randomization as a covariate (Studies 301 and 306B) or a Wilcoxon Rank Sum test (Study 302).

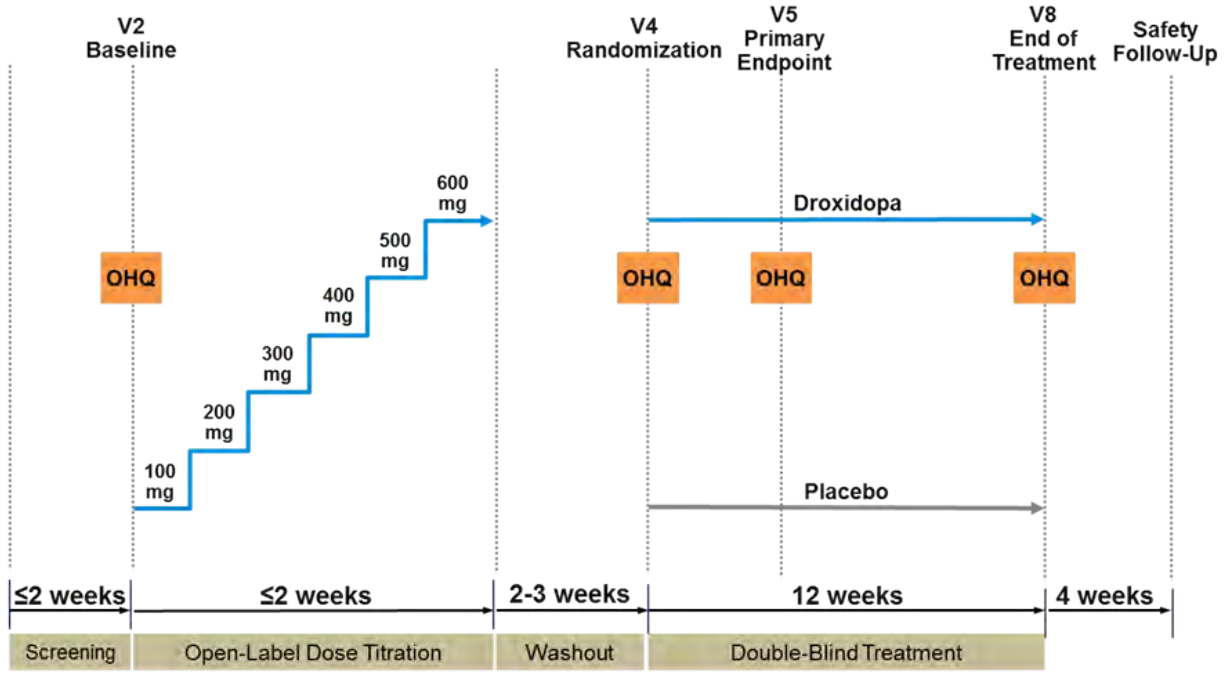
Results from long-term studies (Study 303 following up to 12 months of open-label treatment and Study 306 following up to 2 months of double-blind treatment) provide suggestive evidence that the benefits of droxidopa on both symptoms and standing BP are durable. To confirm the long-term efficacy of droxidopa, Chelsea is conducting a large, 450 patient randomized-controlled study (intended for post-marketing) to confirm the findings generated thus far from the droxidopa development program.

The totality of data from the Sponsor's clinical development program provides substantial evidence that droxidopa is effective for the short-term treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

6.4 Proposed Post-Marketing Study (Study 401)

The Sponsor is currently conducting a randomized placebo-controlled study to further characterize short-term benefit as well as provide evidence of long-term durability of effect of droxidopa. This study is a multi-center, multi-national, randomized, parallel-group, placebo-controlled, double-blind study with a 17-week (maximum) treatment period consisting of an initial, open-label dose titration (up to 2 weeks), followed by a washout period (up to 3 weeks), followed by a 12-week treatment period on a stable dose (Figure 6-48). The study is planned to enroll 450 patients, with a primary endpoint of change from Baseline to Week 1 in OHSA Item 1. The second efficacy endpoint will be the change from Baseline to Week 12 in OHSA Item 1. Study nOH401 started enrolling patients in December 2013. Topline data are expected in late 2016.

Figure 6-48 Study nOH401: Study Design



OHSA=Orthostatic Hypotension Symptom Assessment; OHQ=Orthostatic Hypotension Questionnaire; V=Visit.

7. OVERVIEW OF SAFETY

The data included within this Briefing Document provide significant additional information on the safety of droxidopa compared with the original NDA as a result of a significant increase in patient exposure to droxidopa. The total number of subjects exposed to droxidopa has increased from 778 to 940. In addition, the safety database now includes 8- to 10-week, placebo-controlled, comparative data from Studies 306B and 306A (hereafter referenced as "Study 306") along with randomized-controlled safety data on dose titration. The type, number, rate, and severity of TEAEs are consistent with and further support the data presented both in the original NDA and Briefing Document, which concluded droxidopa is well tolerated and safe in this patient population.

Droxidopa therapy was generally well tolerated at all doses. Droxidopa treatment was associated with a small increase in the incidence of headache, dizziness, nausea, hypertension, and fatigue. Most TEAEs were mild to moderate in severity, and events were generally considered by Investigators to be unlikely or not related to study drug.

7.1 Safety Data

As described in Section 4, Chelsea's clinical development program to date includes 10 clinical studies that investigated the safety of droxidopa for the treatment of nOH. The 10 studies include:

- 2 completed placebo-controlled, double-blind studies to assess the safety of droxidopa in patients with PD, MSA, PAF, DβH Deficiency, or NDAN, and symptomatic nOH (Studies 301 and 302);
- 2 completed placebo-controlled, double-blind studies to assess the safety of droxidopa in PD patients with symptomatic nOH (Study 306A and Study 306B);
- 2 completed open-label extension studies to assess the long-term safety of droxidopa in patients with PD, MSA, PAF, DβH Deficiency, or NDAN, and symptomatic nOH (Studies 303 and 304);
- a completed 24-hour ambulatory BP monitoring study (Study 305) in a subset of patients originally enrolled in Study 301;
- 2 bioequivalence (BE) studies including a completed PK and definitive food effect study in healthy volunteers (Study 101) and a BE study on the 300 mg dose form (Study 104); and
- a completed, dedicated thorough QTc study in healthy volunteers (Study 102).

Detailed descriptions of all studies used for the safety analyses are provided in Appendix 2; Section 10.2.

7.1.1 Safety Datasets

The safety profile of droxidopa has been investigated by using both integrated safety datasets as well as data from individual studies, as detailed below.

Integrated safety datasets include:

(1) Placebo-controlled Studies 301 and 302

- Safety data from the double-blind placebo-controlled periods from Study 301 (1 week) and Study 302 (2 weeks) were integrated.
- Safety data from the open-label titration periods from Studies 301 and 302 were integrated.

(2) Placebo-controlled Studies 306A and 306B

(3) All safety data from Study 306A were integrated with all safety data from Study 306B

(4) Long-term Extension Studies 303 and 304

- All clinical safety data from Study 303 (including the 2-week, randomized-withdrawal period) were integrated with all safety data from Study 304.

Non-integrated safety data include:

(1) Study 305: Phase 3, 24-hour ambulatory BP monitoring study

(2) Study 102: Dedicated thorough QTc study

(3) Study 101: Phase 1 BE and fed/fasted PK study

(4) Study 104: Phase 1 BE study of 300 mg dose

Within each of the results sections, the data from the short-term placebo-controlled studies (i.e., integrated data from Studies 301 and 302 followed by data from Study 306) will be presented and discussed first followed by a presentation and discussion of the data from the long-term extension study grouping.

7.2 Extent of Exposure

7.2.1 Summary of Overall Extent of Exposure

A total of 940 subjects have been treated with droxidopa in Chelsea and European DSP-sponsored studies; of these 940 subjects, 820 patients were included in Phase 2 and 3 clinical studies and 120 healthy volunteers were enrolled in Phase 1 studies. Across these studies, patients received doses of droxidopa ranging from 100 mg to 1800 mg/day. In the Phase 2 and 3 clinical studies, a total of 391 patients are estimated to have received at least 6 months of therapy, 263 patients have received at least 1 year of therapy, and 92 patients have received over 2 years of therapy with droxidopa (Table 7-1).

Table 7-1 Estimates of Patient Exposure

	Duration of Exposure to Droxidopa					
	<6 weeks	**≥6 weeks**	**≥3 months**	**≥6 months**	**≥1 year**	**≥2 years**
Total Daily Dose (mg):						
200	28	27	27	25	25	0
300	80	25	16	10	6	2
400	24	21	17	13	9	2
600	151	99	67	56	38	9
900	178	115	100	89	52	24
1200	155	96	85	70	38	15
1500	93	81	64	47	38	16
1800	111	109	100	81	57	24
Total Number of Patients	**820**	**573**	**476**	**391**	**263**	**92**

Subjects enrolled in Studies 101 and 102 are not counted in this table.

7.2.2 Summary of Overall Extent of Exposure in Chelsea-Sponsored Clinical Studies

A total of 638 patients have been treated with droxidopa in Studies 301, 302, 303, 304, and 306. This includes 7 patients in Studies 301 and 302 who discontinued during the open-label titration phase and subsequently re-entered into their respective study with a new subject number. Therefore, the total number of unique droxidopa-treated patients in the Chelsea-sponsored studies is 631. Across these studies, patients received doses of droxidopa ranging from 300 mg to 1800 mg/day. A total of 302 patients received at least 6 months of therapy, 189 patients received at least 1 year of therapy, and 69 patients received at least 2 years of therapy with droxidopa (Table 7-2).

Table 7-2 Summary of Patient Exposure to Droxidopa by Dose in Chelsea-Sponsored Studies

	Droxidopa Average Total Daily TID Dose[1]						
	300 mg (N=56)	**600 mg (N=95)**	**900 mg (N=128)**	**1200 mg (N=155)**	**1500 mg (N=93)**	**1800 mg (N=111)**	**Total (N=638)**
Categorical Duration of Treatment, n (%)							
<6 weeks	56 (100.0)	95 (100.0)	128 (100.0)	155 (100.0)	93 (100.0)	111 (100.0)	638 (100.0)
≥6 weeks	11 (19.6)	59 (62.1)	81 (63.3)	96 (61.9)	81 (87.1)	109 (98.2)	437 (68.5)
≥3 months	8 (14.3)	41 (43.2)	70 (54.7)	85 (54.8)	64 (68.8)	100 (90.1)	368 (57.7)
≥6 months	5 (8.9)	34 (35.8)	65 (50.8)	70 (45.2)	47 (50.5)	81 (73.0)	302 (47.3)
≥1 year	4 (7.1)	22 (23.2)	30 (23.4)	38 (24.5)	38 (40.9)	57 (51.4)	189 (29.6)
≥2 years	2 (3.6)	4 (4.2)	8 (6.3)	15 (9.7)	16 (17.2)	24 (21.6)	69 (10.8)

TID=three times daily.

1 Total duration of treatment was tabulated based on the average daily dose of droxidopa received during Studies 301, 302, 303, 304, and/or 306A and 306B.

7.2.3 Summary of Increased Exposure to Droxidopa Since the Original Submission

Since the original NDA, an additional 162 patients with nOH have been treated with droxidopa in Chelsea-sponsored studies, which includes additional patients from open-label Study 304 and patients from the 8- to 10-week Study 306. The total number of patients who have been exposed to droxidopa for at least 6 months increased from 281 to 391; the number of patients exposed to droxidopa for at least 1 year increased from 167 to 263; and the number of patients exposed to droxidopa for at least 2 years increased from 28 to 92.

Due to the inclusion of patients from Study 304, which was ongoing at the time of the original NDA, the mean duration of exposure in the long-term extension study grouping increased from 239.6 days to 376.1 days, including an upper range of almost 4 years of exposure. During the long-term studies, patients received droxidopa across a range of doses, with the highest proportion (26.8%) receiving 600 mg TID. The increase in mean duration of exposure coupled with the increase in the number of patients included in the long-term extension study grouping (from 301 to 422 patients) resulted in an increase from 197.6 patient-years of exposure to 434.8 patient-years of exposure in this study grouping.

7.3 Patient Demographics

In addition to the presentation of demographic characteristics for individual studies in the efficacy sections above, demographic characteristics are also presented below for the datasets that have been integrated for the safety analyses.

7.3.1 Placebo-Controlled Studies 301 and 302

A summary of demographic and Baseline characteristics for patients enrolled in the RCT phase of Studies 301/302 is presented in Table 7-3.

Table 7-3 Studies 301/302: Summary of Demographics and Baseline Diagnoses during the Randomized Controlled Phase (Safety Set)

	Placebo (N=132)	Droxidopa (N=131)
Primary Clinical Diagnosis, n (%)		
PD	54 (40.9)	56 (42.7)
MSA	25 (18.9)	31 (23.7)
PAF	38 (28.8)	34 (26.0)
DβH Deficiency	1 (0.8)	0
NDAN	9 (6.8)	4 (3.1)
Other	5 (3.8)	6 (4.6)
Age (years) at Screening		
Mean (SD)	60.0 (17.87)	59.5 (16.02)
Min, Max	18, 88	20, 88
Gender, n (%)		
Male	75 (56.8)	71 (54.2)
Female	57 (43.2)	60 (45.8)
Region, n (%)		
US	65 (49.2)	57 (43.5)
Non-US	67 (50.8)	74 (56.5)
Race, n (%)		
White	124 (93.9)	130 (99.2)
Black/African-American	1 (0.8)	0
Asian	2 (1.5)	1 (0.8)
American Indian/Alaskan Native	1 (0.8)	0
Hispanic/Latino	4 (3.0)	0
Weight (kg), n	**130**	**130**
Mean (SD)	74.21 (14.323)	75.09 (16.941)
Min, Max	38.6, 110.0	46.0, 183.0

DβH=dopamine beta hydroxylase; Max=maximum; Min=minimum; MSA=Multiple System Atrophy; NDAN=Non-Diabetic Autonomic Neuropathy; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; SD=standard deviation.

7.3.2 Study 306

A summary of demographic and Baseline characteristics for patients enrolled in Study 306 overall is presented in Table 7-4.

Table 7-4 Study 306: Summary of Demographic and Baseline Characteristics (Safety Set)

	Placebo (N=108)	Droxidopa (N=114)
Sex [n (%)]		
Male	68 (63.0)	77 (67.5)
Female	40 (37.0)	37 (32.5)
Race [n (%)]		
White	102 (94.4)	110 (96.5)
Black/African American	3 (2.8)	2 (1.8)
Asian	0	1 (0.9)
Hispanic/Latino	3 (2.8)	1 (0.9)
Region [n (%)]		
US	108 (100.0)	114 (100.0)
Non-US	0	0
Age (Years) at Screening		
Mean (SD)	72.36 (8.010)	72.55 (7.452)
Min, Max	52.9, 86.3	41.4, 91.7
Weight (kg)		
Mean (SD)	76.28 (15.587)	76.94 (16.649)
Min, Max	38.6, 122.3	46.4, 122.0

Kg=kilograms; Max=maximum; Min=minimum; SD=standard deviation; US=United States.

7.3.3 Long-Term Extension Study Grouping

A summary of demographic and Baseline characteristics for the long-term extension study grouping is presented in Table 7-5.

Table 7-5 Long-term Extension Study Grouping: Summary of Demographic and Baseline Characteristics (Safety Set)

	Total Droxidopa (N=422)
Primary Clinical Diagnosis [n (%)]	
PD	265 (62.8)
MSA	55 (13.0)
PAF	78 (18.5)
DβH Deficiency	1 (0.2)
NDAN	12 (2.8)
Other	9 (2.1)
Missing	2 (0.5)
Sex [n (%)]	
Male	253 (60.0)
Female	169 (40.0)

	Total Droxidopa (N=422)
Age (Years) at Screening	
Mean (SD)	65.3 (14.68)
Min, Max	18, 90
Race [n (%)]	
White	406 (96.2)
Black/African-American	4 (0.9)
Asian	3(0.7)
American Indian/Alaskan Native	1 (0.2)
Hispanic/Latino	8 (1.9)
Weight (kg, n=421)	
Mean (SD)	75.78 (15.906)
Min, Max	38.6, 183.0
Region [n (%)]	
US	290 (68.7)
Non-US	132 (31.3)

DβH=dopamine beta hydroxylase; kg=kilograms; Max=maximum; min=minimum; MSA=Multiple System Atrophy; NDAN=Non-Diabetic Autonomic Neuropathy; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; SD=standard deviation; US=United States.
Note: Errors in data entry of weight were identified post database lock. Data are presented as recorded in the final study database.

7.4 Adverse Events

7.4.1 Common Adverse Events

7.4.1.1 Short-Term Placebo-Controlled Studies

The most common TEAEs were consistent across the short-term placebo-controlled studies (Studies 301/302 and 306) and are presented in Table 7-6. A higher proportion of patients on droxidopa experienced headache, dizziness, nausea, and hypertension compared with placebo across all studies.

The most common TEAE reported in the placebo-controlled studies was headache (Studies 301/302: 6.1% of droxidopa-treated patients and 3.0% of placebo-treated patients; Study 306: 13.2% of droxidopa-treated patients and 7.4% of placebo-treated patients). The second most common TEAE was dizziness (Studies 301/302: 3.8% of droxidopa-treated patients and 1.5% of placebo-treated patients; Study 306: 9.6% of droxidopa-treated patients and 4.6% placebo-treated patients). The increased incidence of the TEAE of dizziness may be a function of patients' increased activity and increased predisposition to experiencing dizziness. See Section 7.5.2 for a discussion of hypertension.

Table 7-6 Studies 301/302 and Study 306: Most Common TEAEs (≥5% of Patients in the Droxidopa or Placebo Groups) (Safety Sets)

	Study 301 and Study 302 (1-2 week RCT Phase)		Study 306 (8-10 Week RCT Phase)	
Preferred Term	**Placebo (N=132) n (%)**	**Droxidopa (N=131) n (%)**	**Placebo (N=108) n (%)**	**Droxidopa (N=114) n (%)**
Patients with TEAEs Overall (%)	**31 (23.5)**	**30 (22.9)**	**87 (80.6)**	**91 (79.8)**
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Fatigue	3 (2.3)	2 (1.5)	6 (5.6)	8 (7.0)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)
Contusion	0	0	12 (11.1)	6 (5.3)
Excoriation	1 (0.8)	0	8 (7.4)	6 (5.3)
Oedema peripheral	2 (1.5)	0	6 (5.6)	5 (4.4)
Skin laceration	0	1 (0.8)	10 (9.3)	5 (4.4)
Blood pressure increased	0	0	7 (6.5)	4 (3.5)
Diarrhoea	1 (0.8)	1 (0.8)	8 (7.4)	4 (3.5)
Back pain	0	0	6 (5.6)	3 (2.6)
Fall[1]	9 (6.8)	1 (0.8)	1 (0.9)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

1 In Study 306 Investigators were instructed not to record a fall as an AE.

As expected, higher percentages of patients in Study 306, which had a 8- to 10-week RCT phase, experienced TEAEs overall as well as TEAEs meeting the most common definition compared with Studies 301/302 (Table 7-6), studies that had RCT phases of 1 and 2 weeks, respectively. When duration of exposure was taken into account (number of patients multiplied by mean exposure; Table 7-7), the rates (based on events per patient-years) for TEAEs overall and for TEAEs meeting the most common definition were comparable between Study 306 and Studies 301/302, with the exception of fall. Of note, in Study 306, Investigators were instructed not to record a fall as a TEAE since falls were to be recorded in the electronic patient diaries; Investigators were to only record injuries caused by falls as TEAEs. Consequently, the increased number of events observed in Study 306 compared with Studies 301/302 is associated with the increased cumulative observation period and is not associated with increasing rates of TEAEs as a result of patients being exposed to droxidopa for longer periods of time.

Table 7-7 Studies 301/302 and Study 306: Exposure-Adjusted Rate of the Most Common TEAEs (≥5% of Patients in the Droxidopa or Placebo Groups) (Safety Sets)

	Study 301 and Study 302 (1-2 week RCT Phase)				Study 306 (8-10 Week RCT Phase)			
	Placebo (N=132) 3.88 patient-years		Droxidopa (N=131) 4.06 patient-years		Placebo (N=108) 17.81 patient-years		Droxidopa (N=114) 16.87 patient-years	
Preferred Term	**E**	**Rate[1]**	**E**	**Rate[1]**	**E**	**Rate[1]**	**E**	**Rate[1]**
Number of TEAEs and Rate of TEAEs	**58**	**14.95**	**63**	**15.52**	**258**	**14.49**	**291**	**17.25**
Headache	4	1.03	9	2.22	8	0.45	19	1.13
Dizziness	2	0.52	5	1.23	6	0.34	13	0.77
Nausea	2	0.52	2	0.49	5	0.28	13	0.77
Fatigue	3	0.77	2	0.49	7	0.39	8	0.47
Hypertension	0	0	2	0.49	2	0.11	11	0.65
Contusion	0	0	0	0	14	0.79	7	0.41
Excoriation	1	0.26	0	0	8	0.45	6	0.36
Oedema peripheral	2	0.52	0	0	6	0.34	5	0.30
Skin laceration	0	0	1	0.25	15	0.84	10	0.59
Blood pressure increased	0	0	0	0	7	0.39	9	0.53
Diarrhoea	2	0.52	1	0.25	9	0.51	4	0.24
Back pain	0	0	0	0	6	0.34	3	0.18
Fall	10	2.58	2	0.49	1	0.06	0	0

AE=adverse event; E=event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Events are counted each time in the event (E) column. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

1 Rate of AE is calculated by the number of events per patient per year of mean exposure. Exposure for Studies 301/302 was 4.06 patient years for droxidopa (n=131 x [mean days of exposure of 11.3 days/365]) and 3.88 patient years for placebo (n=132 x [mean exposure of 10.7 days/365]). Exposure for Study 306 was 16.87 patient years for droxidopa (n=114 x [mean days of exposure of 54.0 days/365]) and 17.81 patient years for placebo (n=108 x [mean exposure of 60.2 days/365]).

7.4.1.1.1 Treatment-Emergent AEs During Titration

A summary of the most common TEAEs that occurred during the open-label titration period of Studies 301/302 is presented in Table 7-8.

In Studies 301/302, during the open-label titration period, a total of 206 patients (46.4%) reported at least 1 TEAE. The most commonly reported TEAEs were headache (10.4%), dizziness (7.2%), nausea (4.5%), fatigue (4.3%), and fall (4.1%).

Table 7-8 Studies 301/302: Most Common TEAEs (≥3% of Patients in the Droxidopa Group) During the Titration Phase (Safety Sets)

Preferred Term	Study 301 and Study 302 (Open-Label Titration) Droxidopa (N=444[1]) n (%)
Patients with TEAEs Overall (%)	**206 (46.4)**
Headache	46 (10.4)
Dizziness	32 (7.2)
Nausea	20 (4.5)
Fatigue	19 (4.3)
Fall	18 (4.1)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).
1 Includes 181 non-randomized patients and 263 randomized patients (132 randomized to placebo and 131 randomized to droxidopa.

Study 306 included a blinded placebo-controlled titration phase to better characterize the safety of droxidopa during dose optimization. As noted above, Studies 301 and 302 had only collected these data in single-arm, open-label titration phases. A summary of the most common TEAEs that occurred during the titration and treatment phases is presented in Table 7-9. During titration, the incidence of TEAEs overall was higher in the droxidopa group (63 patients [55.3%]) compared with the placebo group (47 patients [43.5%]). Headache, dizziness, nausea, fatigue, hypertension, and insomnia were also the most commonly reported (>3%) TEAEs during titration. Of these TEAEs, all occurred at higher incidences in the droxidopa group compared with the placebo group. Headache, dizziness, nausea, and fatigue were also the most commonly reported TEAEs during the open-label titration period of Studies 301/302.

During the treatment phase of Study 306, TEAEs overall occurred at a similar incidence in the droxidopa group (58 patients [61.7%]) compared with the placebo group (68 patients [66.0%]). The most common TEAEs that occurred during the treatment phase are presented in Table 7-9.

Table 7-9 Study 306: Most Common TEAEs (≥3% of Patients in the Droxidopa Group) During the Titration and Treatment Phase (Safety Sets)

Preferred Term	Study 306	
Double-Blind Titration Phase	**Placebo (N=108)**	**Droxidopa (N=114)**
Patients with TEAEs Overall (%)	**47 (43.5)**	**63 (55.3)**
Headache	5 (4.6)	12 (10.5)
Dizziness	1 (0.9)	7 (6.1)
Nausea	5 (4.6)	8 (7.0)
Fatigue	5 (4.6)	7 (6.1)
Insomnia	1 (0.9)	5 (4.4)
Hypertension	0	5 (4.4)
Treatment Phase[1]	**Placebo (N=103)**	**Droxidopa (N=94)**
Patients with TEAEs Overall (%)	**68 (66.0)**	**58 (61.7)**
Headache	3 (2.9)	5 (5.3)
Hypertension	1 (1.0)	5 (5.3)
Contusion	11 (10.7)	5 (5.3)
Excoriation	6 (5.8)	5 (5.3)
Skin laceration	8 (7.8)	4 (4.3)
Dizziness	4 (3.9)	4 (4.3)
Urinary tract infection	5 (4.9)	3 (3.2)
Edema peripheral	4 (3.9)	3 (3.2)
Dehydration	1 (1.0)	3 (3.2)
Blood pressure increased	6 (5.8)	3 (3.2)

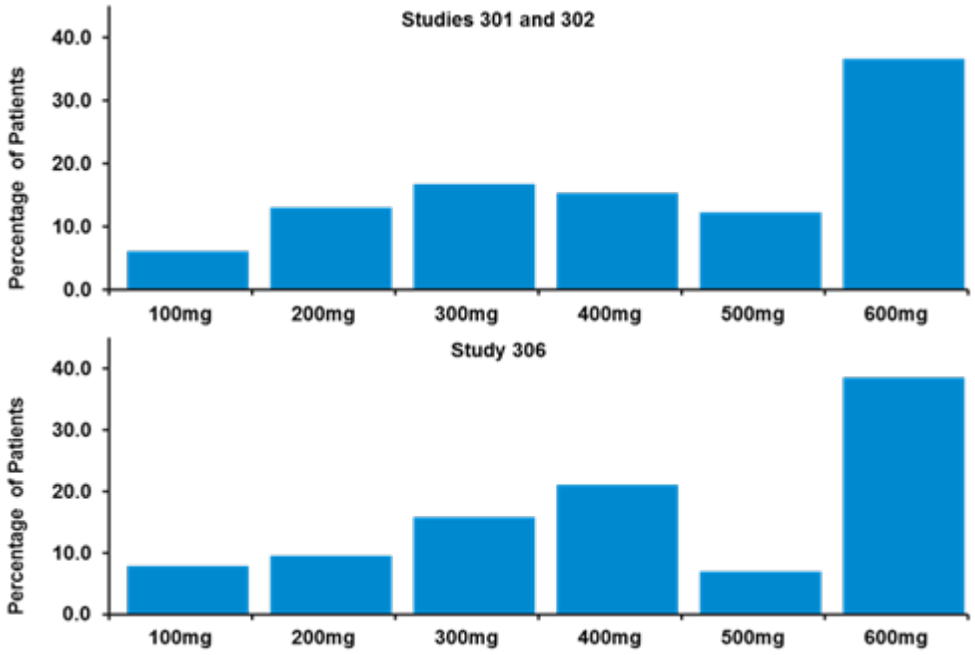
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0.
1 Patient 153007 was randomized to placebo but received some droxidopa. As a result, this patient is included in the droxidopa treatment arm.

7.4.1.1.2 Treatment-Emergent AEs by Dose of Droxidopa

A display of the number of patients who received droxidopa by dose in Studies 301/302 and Study 306 is provided in Figure 7-1.

Overall, there was a similar distribution of patients across the 100 mg TID to 500 mg TID droxidopa dose groups, while a comparatively higher proportion of patients received droxidopa 600 mg TID, which is not unexpected given the forced titration design of the short-term placebo controlled studies.

Figure 7-1 Studies 301/302 and Study 306: Patient Distribution by Dose



A summary of TEAEs overall by dose in Studies 301/302 and Study 306 is presented in Table 7-10. In both Studies 301/302 and Study 306, there was no association between the incidence of TEAEs and the dose of droxidopa administered.

Table 7-10 Studies 301/302 and Study 306: Summary of TEAEs by Dose (Safety Sets)

Study 301 and Study 302 (1-2 week RCT Phase)		Study 306 (8-10 Week RCT Phase)	
Droxidopa Dose (TID)	**TEAEs n (%)**	**Droxidopa Dose (TID)**	**TEAEs n (%)**
Placebo (n=132)	31 (23.5)	Placebo (n=108)	87 (80.6)
100 mg (n=8)	2 (25.0)	100 mg (n=9)	8 (88.9)
200 mg (n=17)	5 (29.4)	200 mg (n=11)	8 (72.7)
300mg (n=22)	5 (22.7)	300 mg (n=18)	15 (83.3)
400 mg (n=20)	2 (10.0)	400 mg (n=24)	21 (87.5)
500 mg (n=16)	6 (37.5)	500 mg (n=8)	5 (62.5)
600 mg (n=48)	10 (20.8)	600 mg (n=44)	34 (77.3)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; TEAE=treatment-emergent adverse event; TID=three times daily.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

7.4.1.2 Long-Term Extension Study Grouping

The most common TEAEs in the long-term extension study grouping are presented in Table 7-11.

The long-term extension studies displayed a similar pattern of common TEAEs compared with the placebo-controlled studies, and this pattern is similar to those that would be expected in the patient population enrolled in the study. The most common TEAEs were fall (23.5%), urinary tract infection (14.7%), headache (13.3%), syncope (12.6%), and dizziness (10.0%). Hypertension was reported by 4.5% of patients in the long-term extension study grouping; however, the exposure-adjusted rate for this TEAE was only 0.05 events per patient-year.

Table 7-11 Long-Term Extension Study Grouping: Most Common TEAEs (≥5% of Patients) (Safety Set)

Preferred Term	Study 303 and Study 304 (Long-Term Studies) Droxidopa (N=422) n (%)
Patients with TEAEs Overall (%)	**321 (76.1)**
Fall	99 (23.5)
Urinary tract infection	62 (14.7)
Headache	56 (13.3)
Syncope	53 (12.6)
Dizziness	42 (10.0)
Back pain	31 (7.3)
Fatigue	30 (7.1)
Nausea	27 (6.4)
Asthenia	27 (6.4)
Constipation	21 (5.0)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.
Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 10.1.

As expected, higher percentages of patients in the long-term extension studies experienced TEAEs overall as well as TEAEs meeting the most common definition compared with the placebo-controlled studies (Table 7-6). When duration of exposure was taken into account (number of patients multiplied by mean exposure; Table 7-12), exposure-adjusted rates (based on events per patient-years) for TEAEs overall and for TEAEs meeting the most common definition in the long-term extension study grouping were low overall (<0.5 events per patient-year) and were generally lower compared with Studies 301/302 and Study 306 (Table 7-7).

Table 7-12 Long-Term Extension Study Grouping: Exposure-Adjusted Rates of the Most Common TEAEs (≥5% of Patients) (Safety Set)

Preferred Term	Study 303 and Study 304 (Long-Term Studies) Total Droxidopa (N=422) 434.83 patient years E	Rate[1]
Number of TEAEs and Rate of TEAEs	**2562**	**5.89**
Fall	191	0.44
Urinary tract infection	142	0.33
Headache	75	0.17
Syncope	75	0.17
Dizziness	66	0.15
Back pain	39	0.09
Fatigue	33	0.08
Nausea	31	0.07
Asthenia	28	0.06
Constipation	21	0.05

AE=adverse event; E=event; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Events are counted each time in the event (E) column. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 10.1.

1 Rate of AE is calculated by the number of events per patient per year of mean exposure. Exposure for Studies 303/304 was 434.83 patient years (n=422 x [mean exposure of 376.1 days/365]).

7.4.2 Deaths

A total of 27 deaths occurred across the Sponsor's clinical studies (Table 7-13). Twelve of the 27 deaths (44.4%) occurred in PD patients. Despite the fact that only a minority of enrolled patients had a diagnosis of MSA (21.4% in Studies 301/302 and 13.0% in the long-term extension study grouping), 13 of the 27 deaths (48.1%) occurred in MSA patients. MSA is a serious disease associated with a high background mortality rate.

Table 7-13 By-Patient Summary of Fatal SAEs (Safety Set)

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]
Study 301									
Study 302									
114002 [3]	58	M	MSA	Unknown	N/A – Prior to Treatment	N/A	Unknown	N/A	N/A
114003 [3]	63	F	MSA	Cardiopulmonary Arrest	N/A - Discontinued	13/2	ND	Not related	N/A
Study 303									
129002	63	F	MSA	Sudden cardiac death	200 mg	286/ 1	Severe	Not related	None
130002	60	M	MSA	Hypoxic encephalopathy	400 mg	71/ 16	Severe	Possibly	Disc
136001	57	M	PD	Pneumonia	100 mg	539/ 33	Moderate	Not related	Disc
136002	81	F	PD	Acute respiratory failure	400 mg	414/ 24	Severe	Not related	Disc
141001	88	M	PD	Pelvic fracture	600 mg	247/ 8	Severe	Unlikely	Disc
Study 304 [4]									
103005	61	M	MSA	Respiratory failure	600 mg	598/3	Severe	Not related	None
103007	57	M	MSA	Carotid artery thrombosis	600 mg	146/1	Severe	Unlikely	None
105007	56	F	MSA	Circulatory collapse	500 mg	128/1	Moderate	Not related	Disc
113003A	62	M	PAF	Myocardial infarction	600 mg	550/1	Severe	Not related	Disc
113006A	53	M	MSA	Multiple system atrophy	600 mg	777/1	Severe	Not related	None
115004A	75	M	NDAN	Myocardial infarction	400 mg	363/1	Severe	Possibly	Disc
116002	61	F	PD	Respiratory failure	600 mg	1033/1	Severe	Not related	Disc
116006	70	F	MSA	Acute respiratory failure	600 mg	443/5	Severe	Not related	Disc
116009	73	M	MSA	Subdural hemorrhage	600 mg	ND[5]/ND	Severe	Not related	Disc
125002 [3]	78	M	PD	Unknown cause	600 mg	439 / ND	ND	ND	ND
125006	79	M	MSA	Sepsis	800 mg/day [6]	453/20	Severe	Not related	Disc
125010	80	M	PD	Cardio-respiratory arrest	600 mg	37/2	Severe	Unlikely	Disc
126009	79	M	PD	Pneumonia aspiration	600 mg	735/2	Severe	Not related	Disc
132023Z	83	F	PD	Respiratory failure	400 mg 100 days prior to respiratory failure	189/1	Severe	Not related	Disc
145001Z	78	M	PD	Cardio-respiratory arrest	200 mg	104/1	Severe	Unlikely	Disc
146001A	85	M	PD	Respiratory arrest	600 mg	549/9	Severe	Not related	None

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]
146004A	83	F	PD	Cardiac arrest	600 mg	530/1	Severe	Not related	Disc
168004A[3]	62	M	PD	Urosepsis	600 mg	500/1	ND	Not related	None
501003	55	F	MSA	Brain edema	500 mg	51/5	Severe	Not related	None
503004	60	F	MSA	Pneumonia	300 mg	169/17	Severe	Possibly	Disc
Study 306									
None									

AE=adverse event; Disc=discontinued; F=female; M=male; MSA=Multiple System Atrophy; ND=not determined; NDAN=Non-Diabetic Autonomic Neuropathy; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; Prim. Diag.=primary diagnosis; SAE=serious adverse event; TID=three times daily.

Note: This appendix includes all fatal SAEs captured in the databases of Studies 301, 302, 303, 304, and 306. In addition, any deaths not captured in the database (occurred outside the pre-specified 7-day reporting window) that the Sponsor is aware of are included for completeness.

Note: Due to the titration design of the studies, adjustments to doses as allowed in the protocols, and up-titration occurring in the evening after a study visit with assessments at the previous dose, determining a patient's exact dose can be problematic for some patients. These tables represent the best estimate of dose at time of event drawn from by-patient listings of study medication, visit dates, AEs, and titration visits.

Note: For patients who died, the dose at time of event is the last dose prior to the event.

1 Study day equals day of onset of AE minus first day of treatment +1.

2 Drug action taken: disc=study drug discontinued; incr=study drug dose increased; inter=study drug interrupted; none=no interruption of study drug.

3 Four deaths were not captured in their respective study database: Patient 114002 (death occurred prior to completing Screening; Study 302); Patient 114003 (death occurred after treatment discontinuation and was not entered into study database, information from the CIOMS is included here; Study 302); Patient 125002 (death noted in Study 304 follow-up listing); Patient 168004A experienced a fatal SAE of urosepsis 23 days after discontinuation of study drug due to an SAE of dehydration.

4 Patient ID numbers were unique to individual studies, not to the entire development program, and duplication of patient ID numbers exist. To prevent confusion, patients who entered Study 304 from Study 303 are marked with an "A" at the end of their patient ID and patients from Study 306 were marked with a "Z". Caution should be exercised when aggregating data across studies given the potential for miscounting of subjects.

5 Patient 116009 did not have a recorded start date for the AE leading to death.

6 Patient 125006 took doses of 200 mg, 200 mg, then 400 mg droxidopa daily.

7.4.3 All Serious Adverse Events

Across the droxidopa clinical development program, no single SAE type occurred consistently or in a large enough proportion of patients to suggest a safety concern. In general, the most common SAEs were typical for this population of patients who are elderly and have multiple comorbidities in addition to their nOH.

A discussion of SAEs that occurred in the short-term placebo-controlled studies and in the long-term extension studies is provided below. A listing of all SAEs that occurred is presented by-patient in Appendix 5 (Section 10.5). This listing includes by-patient demographic information; the SAE preferred term; dose of droxidopa at the time of the SAE; severity of the SAE; potential relatedness of the SAE; and outcome of the event.

7.4.3.1 SAEs in the Short-Term Placebo-Controlled Studies

No droxidopa-treated patients reported an SAE in the RCT phase of Studies 301/302 (Table 7-14). In Study 306, 5 patients (4.4%) in the droxidopa group reported a total of 9 SAEs, and 4 patients (3.7%) in the placebo group reported a total of 5 SAEs (Table 7-14). The only SAE reported by more than 1 patient in Study 306 was syncope (2 patients [1.9%] in the placebo group).

Table 7-14 Studies 301/302 and Study 306: SAEs (Safety Sets)

Preferred Term	Study 301 and Study 302 (1-2 week RCT Phase) Placebo (N=132) n (%)	Study 301 and Study 302 (1-2 week RCT Phase) Droxidopa (N=131) n (%)	Study 306 (8-10 Week RCT Phase) Placebo (N=108) n (%)	Study 306 (8-10 Week RCT Phase) Droxidopa (N=114) n (%)
Patients with SAEs Overall	**1 (0.8)**	**0**	**4 (3.7)**	**5 (4.4)**
Syncope	0	0	2 (1.9)	0
Abdominal pain upper	0	0	0	1 (0.9)
Atrial fibrillation	0	0	0	1 (0.9)
Bronchitis viral	0	0	0	1 (0.9)
Faecaloma	0	0	0	1 (0.9)
Inguinal hernia	0	0	0	1 (0.9)
Hypertension	0	0	0	1 (0.9)
Mental status changes	1 (0.8)	0	0	1 (0.9)
Presyncope	0	0	0	1 (0.9)
Upper respiratory tract infection bacterial	0	0	0	1 (0.9)
Asthenia	0	0	1 (0.9)	0
Fibula fracture	0	0	1 (0.9)	0
Viral infection	0	0	1 (0.9)	0
Urinary traction infection	1 (0.8)	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included based on the treatment received prior to the onset of the event. If a patient had multiple occurrences of a TEAE during the same treatment phase, the patient was included only once in the respective patient count. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

1 All SAEs that were reported in Study 306 overall occurred in Study 306B; however, percentages were calculated based on the total number of patients enrolled in Study 306A and Study 306B combined (i.e., placebo [n=108]; droxidopa [n=114]).

7.4.3.2 SAEs in the Long-Term Extension Study Grouping

In the long-term extension study grouping, 105 of 422 patients (24.9%) reported SAEs (Table 7-15). Most events in the long-term extension study grouping were considered to be unlikely or not related to study drug (>85%), required no change in study drug (>55%), and were resolved (>75%; Appendix 5 [Section 10.5]). Approximately 20% of the events resulted in discontinuation of study drug. The most commonly reported SAEs were syncope (14 patients [3.3%]), pneumonia (9 patients [2.1%]), dehydration (8 patients [1.9%]), hip fracture (6 patients [1.4%]), and fall and urinary tract infection (5 patients each [1.2%]).

Table 7-15 Long-Term Extension Study Grouping: Most Common SAEs (≥1% of Patients) (Safety Set)

Preferred Term	Study 303 and Study 304 (Long-Term Studies) Droxidopa (N=422) n (%)
Patients with SAEs Overall (%)	**105 (24.9)**
Syncope	14 (3.3)
Pneumonia	9 (2.1)
Dehydration	8 (1.9)
Hip fracture	6 (1.4)
Urinary tract infection	5 (1.2)
Fall	5 (1.2)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 10.1.

7.4.4 Adverse Events Leading to Discontinuation

Overall, the proportion of patients discontinuing droxidopa due to a TEAE was low in both the short-term placebo-controlled studies in the long-term extension study grouping. There was no consistent pattern in the type of TEAE leading to discontinuation, with the possible exception of hypertension (see Section 7.5.2).

A discussion of TEAEs leading to discontinuation that occurred in the short-term placebo-controlled studies and in the long-term extension studies is provided below. A listing of all TEAEs leading to discontinuation that occurred is presented by-patient in Appendix 6 (Section 10.6). This listing includes by-patient demographic information; the preferred term of the TEAE leading to discontinuation; dose of droxidopa at the time of the TEAE; severity of the TEAE; potential relatedness of the TEAE; and outcome of the event that led to discontinuation.

7.4.4.1 TEAEs Leading to Discontinuation in the Short-Term Placebo-Controlled Studies

No droxidopa-treated patients and 2 placebo-treated patients (1.5%) discontinued from the RCT phase of Studies 301/302 (Table 7-16).

In Study 306, more patients in the droxidopa group discontinued due to a TEAE compared with the placebo group (droxidopa: 10.5%; placebo: 4.6%; Table 7-16). The most common TEAEs that resulted in discontinuation were hypertension (droxidopa: 3 patients [2.6%]; placebo: 1 patient [0.9%]) and blood pressure increased (droxidopa: 2 patients [1.8%]; placebo: 1 patient [0.9%]). No other TEAE leading to discontinuation occurred in more than 1 patient.

Of note, in Study 306, droxidopa was associated with an increase in the number of discontinuations overall during double-blind titration (droxidopa: 16.7%; placebo: 5.6%); however, discontinuation rates due to TEAEs during titration were similar (droxidopa: 5.3%; placebo: 3.6%). Therefore, the difference in dropout rates between treatment groups does not appear to be primarily caused by a difference in the type or number of TEAEs between treatment arms.

Table 7-16 Studies 301/302 and Study 306: TEAEs Leading to Discontinuation (Safety Sets)

	Study 301 and Study 302 (1-2 week RCT Phase)		Study 306 (8-10 Week RCT Phase)	
Preferred Term	**Placebo (N=132) n (%)**	**Droxidopa (N=131) n (%)**	**Placebo (N=108) n (%)**	**Droxidopa (N=114) n (%)**
Patients with TEAEs Leading to Discontinuation Overall	**2 (1.5)**	**0**	**5 (4.6)**	**12 (10.5)**
Hypertension	0	0	1 (0.9)	3 (2.6)
Blood pressure increased	0	0	1 (0.9)	2 (1.8)
Headache	0	0	0	1 (0.9)
Dizziness	0	0	0	1 (0.9)
Parkinson's disease	0	0	0	1 (0.9)
Hypotension	0	0	0	1 (0.9)
Atrial fibrillation	0	0	0	1 (0.9)
Hallucination	0	0	0	1 (0.9)
Mental status changes	0	0	0	1 (0.9)
Abnormal dreams	0	0	0	1 (0.9)
Abdominal discomfort	0	0	0	1 (0.9)
Vision blurred	0	0	0	1 (0.9)
Cholelithiasis	0	0	0	1 (0.9)
Benign neoplasm of bladder	0	0	0	1 (0.9)
Loss of consciousness	1 (0.8)	0	0	0
Syncope	1 (0.8)	0	1 (0.9)	0
Gastroenteritis	0	0	1 (0.9)	0
Malaise	0	0	1 (0.9)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; RCT=Randomized-Controlled Treatment; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included based on the treatment received prior to the onset of the event. If a patient had multiple occurrences of a TEAE during the same treatment phase, the patient was included only once in the respective patient count. Adverse events were coded using MedDRA version 13.0 (for Study 306) or MedDRA version 10.1 (Studies 301 and 302).

7.4.4.2 TEAEs Leading to Discontinuation in the Long-Term Extension Study Grouping

In the long-term extension study grouping, 63 patients (14.9%) discontinued from open-label droxidopa treatment due to a TEAE. There was a variety of TEAEs leading to discontinuation, none of which accounted for more than 1.0% of the patient population (Table 7-17).

Table 7-17 Long-Term Extension Study Grouping: Most Common TEAEs Leading to Discontinuation (>1 Patient) (Safety Set)

Preferred Term	Study 303 and Study 304 (Long-Term Studies) Droxidopa (N=422) n (%)
Patients with TEAEs Leading to Discontinuation Overall (%)	**63 (14.9)**
Pneumonia	3 (0.7)
Respiratory failure	3 (0.7)
Acute respiratory failure	2 (0.5)
Cardio-respiratory arrest	2 (0.5)
Fall	2 (0.5)
Hallucination	2 (0.5)
Hypertension	2 (0.5)
Hypertension crisis	2 (0.5)
Orthostatic hypotension	2 (0.5)
Myocardial infarction	2 (0.5)
Transient ischemic attack	2 (0.5)
Suicide attempt	2 (0.5)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 10.1.

7.5 Safety Topics of Special Interest

7.5.1 Falls and Fall-related Injuries

Across all placebo-controlled studies, the combination of TEAEs of falls, loss of consciousness, and syncope were more common in patients taking placebo compared with droxidopa. In Study 306, 26.9% of placebo-treated patients experienced a fall-related injury compared with 16.7% of droxidopa-treated patients (Table 7-18). These injuries also included potentially debilitating TEAEs of facial bones fracture, fibula fracture, and traumatic brain injury in a total of 3 placebo-treated patients compared with 0 droxidopa-treated patients.

Table 7-18 Study 306: Treatment-emergent AEs Related to Falls (Safety Set)

System Organ Class Preferred Term	Placebo (N=108) n (%)	E	Droxidopa (N=114) (%)	E
Number of Patients (%) and Number of TEAEs Related to Falls	**29 (26.9)**	**52**	**19 (16.7)**	**36**
Injury, Poisoning, and Procedural Complications	**28 (25.9)**	**47**	**15 (13.2)**	**26**
Excoriation	8 (7.4)	8	6 (5.3)	6
Contusion	12 (11.1)	14	5 (4.4)	6
Skin laceration	10 (9.3)	13	5 (4.4)	10
Laceration	1 (0.9)	1	2 (1.8)	2
Injury	2 (1.9)	2	1 (0.9)	1
Soft tissue injury	0	0	1 (0.9)	1
Facial bones fracture	1 (0.9)	1	0	0
Fall	1 (0.9)	1	0	0
Fibula fracture	1 (0.9)	1	0	0
Head injury	1 (0.9)	1	0	0
Joint sprain	1 (0.9)	1	0	0
Mouth injury	2 (1.9)	2	0	0
Tooth fracture	1 (0.9)	1	0	0
Traumatic brain injury	1 (0.9)	1	0	0
General Disorders and Administration Site Conditions	**0**	**0**	**3 (2.6)**	**3**
Pain	0	0	2 (1.8)	2
Face oedema	0	0	1 (0.9)	1
Musculoskeletal and Connective Tissue Disorders	**3 (2.8)**	**3**	**3 (2.6)**	**3**
Back pain	2 (1.9)	2	2 (1.8)	2
Arthralgia	1 (0.9)	1	1 (0.9)	1
Eye Disorders	**1 (0.9)**	**1**	**1 (0.9)**	**1**
Conjunctival haemorrhage	1 (0.9)	1	1 (0.9)	1
Psychiatric Disorders	**0**	**0**	**1 (0.9)**	**1**
Post-traumatic amnestic disorder	0	0	1 (0.9)	1
Vascular Disorders	**0**	**0**	**1 (0.9)**	**2**
Haematoma	0	0	1 (0.9)	2
Skin and Subcutaneous Tissue Disorders	**1 (0.9)**	**1**	**0**	**0**
Scab	1 (0.9)	1	0	0

AE=adverse event; E=event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=System organ class; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs (TEAEs) are AEs that began (or pre-existing AEs that worsened) after receiving the first dose of study drug. Events are counted each time in the event (E) column. Patients are counted only once for each SOC and PT. Treatment-emergent adverse events occurring on the day of, or the day after, a reported fall may be fall-related. Relevant SOC/PTs were identified through manual review prior to unblinding. Percentages are based on the number of patients in each treatment group. Adverse events were coded using MedDRA version 13.0.

7.5.2 Hypertension and Blood Pressure

While incidences of supine hypertension and TEAEs associated with elevations in BP are low in the database, droxidopa does increase the incidence of these types of TEAEs in this population.

A discussion of TEAEs associated with elevations in BP that occurred in the short-term placebo-controlled studies and in the long-term extension studies is provided below. A listing of all TEAEs related to elevations in BP that occurred in any of the Phase 3 studies is presented by patient in Appendix 7 (Section 10.7).

7.5.2.1 TEAEs Related to Elevations in BP in the Short-Term Placebo-Controlled Studies

In the RCT phase of Studies 301/302, there were 2 droxidopa-treated patients (1.5%) compared with 0 placebo-treated patients who reported BP-related TEAEs.

In Study 306, 13 (11.4%) droxidopa-treated patients experienced a TEAE related to an elevation in BP compared with 9 (8.3%) placebo-treated patients (Table 7-19). Patients treated with droxidopa were more likely to discontinue due to a BP-related AE than patients treated with placebo (4.4% vs. 1.9%).

Table 7-19 Study 306: Summary of TEAEs Related to Elevations in BP (Safety Set)

	Placebo (N=108)						Droxidopa (N=114)					
	TEAEs		SAEs		TEAEs leading to discon.		TEAEs		SAEs		TEAEs leading to discon.	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Total BP-related TEAEs	**9 (8.3)**	**10**	**0**	**0**	**2 (1.9)**	**2**	**13 (11.4)**	**21**	**1 (0.9)**	**1**	**5 (4.4)**	**5**
Hypertension	1 (0.9)	2	0	0	1 (0.9)	1	8 (7.0)	11	1 (0.9)	1	3 (2.6)	3
Blood pressure increased	7 (6.5)	7	0	0	1 (0.9)	1	4 (3.5)	9	0	0	2 (1.8)	2
Blood pressure systolic increased	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0	0	0	0

AE=adverse event; BP=blood pressure; discon=discontinuation; E=event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of a TEAE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 13.0.

Rates of supine hypertension (SBP >180 mmHg at all supine measurements during the OST) were higher in the droxidopa group compared with the placebo group in both the RCT phase of Studies 301/302 integrated (droxidopa: 3.1%; placebo: 1.5%) and Study 306 (droxidopa: 7.9%; placebo: 4.6%; Table 7-20).

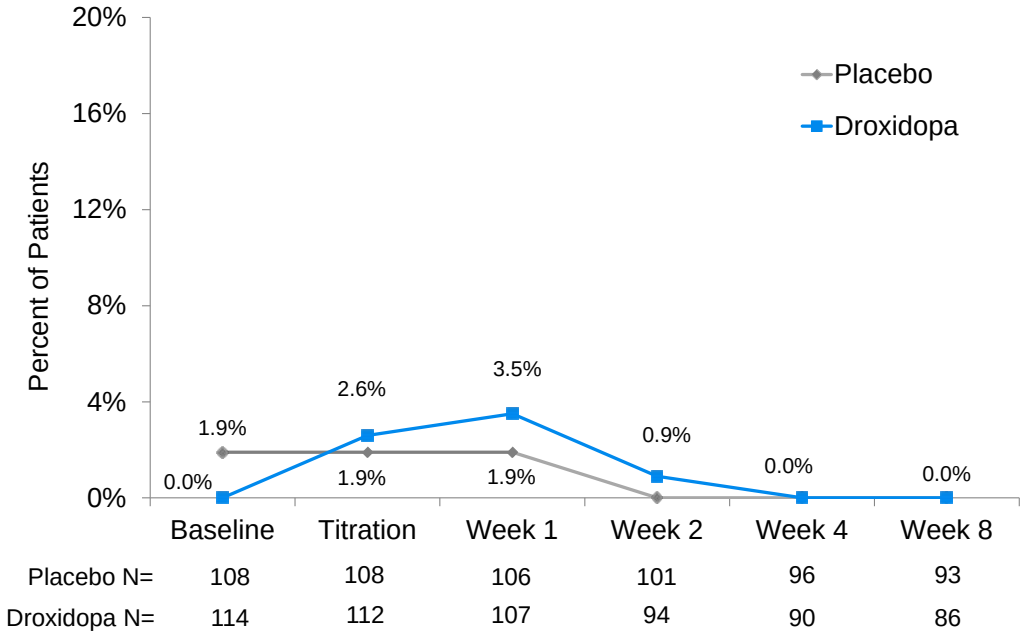
Table 7-20 Studies 301/302 and Study 306: Incidence of Supine Hypertension (>180 mmHg) At All Time Points During the OST by Visit (Safety Sets)

	Placebo	Droxidopa
Study 301/302		
Baseline		
Number of Patients Assessed	131	130
Supine SBP >180 mmHg; n (%)	0	0
End of Study		
Number of Patients Assessed	132	131
Supine SBP >180 mmHg; n (%)	2 (1.5)	4 (3.1)
Study 306		
Baseline		
Number of Patients Assessed	108	114
Supine SBP >180 mmHg; n (%)	2 (1.9)	0
Overall		
Number of Patients Assessed	108	114
Supine SBP >180 mmHg; n (%)	5 (4.6)	9 (7.9)

OST=Orthostatic Standing Test; SBP=systolic blood pressure.

There was no association between the incidence of supine hypertension and duration of treatment with either placebo or droxidopa. Figure 7-2 shows the incidence of patients with supine hypertension at individual visits in Study 306. Of note, the incidences during titration include up to 6 individual titration visits.

Figure 7-2 Study 306: Supine SBP Over Time (Safety Set)



SBP=systolic blood pressure.

7.5.2.2 TEAEs Related to Elevations in BP in the Long-Term Extension Study Grouping

During the long-term extension studies, 31 patients (7.3%) reported TEAEs related to elevations in BP, and 6 patients (1.4%) each reported an SAE and/or a TEAE related to elevations in BP (Table 7-21). The exposure-adjusted rates per patient-year of BP-related TEAEs (0.08), SAEs (0.01), and TEAEs leading to discontinuation (0.01) were low.

The proposed Package Insert has been revised to include a boxed warning regarding supine hypertension as per the Agency's recommendation.

Table 7-21 Long-term Extension Study Grouping: Summary of Exposure-Adjusted Rates for Blood Pressure-Related TEAEs (Safety Set)

	Study 303 and Study 304 (Long-Term Studies) N=422						Study 303 and Study 304 (Long-Term Studies) 434.83 patient-years					
Preferred Term	**TEAEs**		**SAEs**		**TEAEs leading to discontinuation**		**TEAEs**		**SAEs**		**TEAEs leading to discontinuation**	
	n	**%**	**n**	**%**	**n**	**%**	**E**	**Rate[1]**	**E**	**Rate[1]**	**E**	**Rate[1]**
Total BP-related TEAEs	**31**	**7.3**	**6**	**1.4**	**6**	**1.4**	**36**	**0.08**	**6**	**0.01**	**6**	**0.01**
Hypertension	19	4.5	2	0.5	2	0.5	23	0.05	2	0.00	2	0.00
Hypertensive crisis	3	0.7	2	0.5	2	0.5	3	0.01	2	0.00	2	0.00
Blood pressure increased	7	1.7	0	0	1	0.2	8	0.02	0	0.00	1	0.00
Malignant hypertension	1	0.2	1	0.2	1	0.2	1	0.00	1	0.00	1	0.00
Blood pressure fluctuation	1	0.2	1	0.2	0	0	1	0.00	1	0.00	0	0.00

AE=adverse event; BP=blood pressure; E=event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included. If a patient had multiple occurrences of an AE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 10.1.

1 Rate of AE is calculated by the number of events per patient per year of mean exposure. The exposure for the original ISS was 197.59 patient years (n=301 x [mean exposure of 239.6 days/365]). Exposure for the updated ISS is 434.83 patient years (n=422 x [mean exposure of 376.1 days/365])

7.5.3 Cardiovascular Safety

The rate of cardiovascular-related TEAEs was consistently low across studies. Droxidopa may be associated with a small increase in the rate of arrhythmias, although most occurred during open-label treatment, which makes it difficult to draw definitive conclusions regarding causality.

A discussion of cardiovascular-related TEAEs that occurred in the short-term placebo-controlled studies and in the long-term extension studies is provided below. A listing of all cardiovascular-related TEAEs is provided in Appendix 8 (Section 10.8).

7.5.3.1 Cardiovascular-related TEAEs in the Short-Term Placebo-Controlled Studies

No cardiovascular-related TEAEs were reported during the RCT phase of Studies 301/302.

In the droxidopa group in Study 306, 1 patient (0.9%) each reported single TEAEs of atrial fibrillation, sinus bradycardia, supraventricular extrasystoles, tachycardia, and tachycardia paroxysmal (Table 7-22). The TEAE of atrial fibrillation (in Patient 110006) was both serious (Appendix 5 [Section 10.5]) and resulted in study discontinuation (Appendix 6 [Section 10.6]). Of note, this patient was randomized to placebo, but 4 days prior to the SAE of atrial fibrillation, the patient errantly received droxidopa therapy over a 3-day period without incident. The patient was returned to placebo therapy and treated for 2 days prior to the SAE. In the placebo group, 1 patient (0.9%) each reported single TEAEs of sinus bradycardia, tachycardia, and chest discomfort; none of these events were serious or resulted in study discontinuation.

Table 7-22 Study 306: Summary of Cardiovascular-Related TEAEs (Safety Set)

	Placebo (N=108)						Droxidopa (N=114)					
	TEAEs		SAEs		TEAEs leading to discon.		TEAEs		SAEs		TEAEs leading to discon.	
Preferred Term	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
SOC of Cardiac Disorders	**2 (1.9)**	**2**	**0**	**0**	**0**	**0**	**5 (4.4)**	**5**	**1 (0.9)**	**1**	**1 (0.9)**	**1**
Atrial fibrillation	0	0	0	0	0	0	1 (0.9)	1	1 (0.9)	1	1 (0.9)	1
Sinus bradycardia	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0	0	0	0
Supraventricular extrasystoles	0	0	0	0	0	0	1 (0.9)	1	0	0	0	0
Tachycardia	1 (0.9)	1	0	0	0	0	1 (0.9)	1	0	0	0	0
Tachycardia paroxysmal	0	0	0	0	0	0	1 (0.9)	1	0	0	0	0
SOC General disorders and administration site conditions	**1 (0.9)**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Chest discomfort	1 (0.9)	1	0	0	0	0	0	0	0	0	0	0

AE=adverse event; BP=blood pressure; discon=discontinuation; E=event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of a TEAE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 13.0.

7.5.3.2 Cardiovascular-related TEAEs in the Long-Term Extension Study Grouping

During the long-term extension studies, 32 patients (7.6%) reported TEAEs in the Cardiac Disorders System Organ Class (SOC), 7 patients (1.7%) reported cardiac-related TEAEs in the General Disorders and Administration Site Conditions SOC, and 6 patients (1.4%) reported cardiac-related TEAEs in the Vascular Disorders SOC (Table 7-23). The only TEAE reported by ≥1.0% of patients was atrial fibrillation (7 patients [1.7%]). The only cardiovascular-related SAEs reported by >1 patient were atrial fibrillation (3 subjects [0.7%]) and angina, cardio-respiratory arrest, myocardial infarction, and hypertensive crisis (2 patients each [0.5%]), and the only cardiovascular-related TEAEs that led to discontinuation in >1 patient were the SAEs of cardio-respiratory arrest, myocardial infarction, and hypertensive crisis (2 patients each [0.5%]).

Table 7-23 Long-term Extension Study Grouping: Summary of Cardiovascular-related TEAEs (Safety Set)

	Total Droxidopa (N=422)		
System Organ Class Preferred Term	**TEAEs n [%]**	**SAEs n [%]**	**TEAEs Leading to Discontinuation n [%]**
Cardiac Disorders	**32 (7.6)**	**14 (3.3)**	**8 (1.9)**
Atrial fibrillation	7 (1.7)	3 (0.7)	1 (0.2)
Atrioventricular block first degree	4 (0.9)	0	0
Angina pectoris	3 (0.7)	2 (0.5)	0
Ventricular extrasystoles	3 (0.7)	0	1 (0.2)
Atrial flutter	2 (0.5)	1 (0.2)	0
Bradycardia	2 (0.5)	1 (0.2)	0
Bundle branch block left	2 (0.5)	0	0
Cardio-respiratory arrest	2 (0.5)	2 (0.5)	2 (0.5)
Myocardial infarction	2 (0.5)	2 (0.5)	2 (0.5)
Palpitations	2 (0.5)	0	0
Sinus bradycardia	2 (0.5)	0	0
Supraventricular extrasystoles	2 (0.5)	0	0
Tachycardia	2 (0.5)	0	0
Arrhythmia	1 (0.2)	0	0
Atrial tachycardia	1 (0.2)	0	0
Cardiac arrest	1 (0.2)	1 (0.2)	1 (0.2)
Cardiac failure congestive	1 (0.2)	1 (0.2)	1 (0.2)
Cardiomegaly	1 (0.2)	0	0
Conduction disorder	1 (0.2)	0	0
Coronary artery disease	1 (0.2)	1 (0.2)	0
Supraventricular tachycardia	1 (0.2)	1 (0.2)	0
Vascular Disorders	**6 (1.4)**	**5 (1.2)**	**4 (0.9)**
Circulatory collapse	1 (0.2)	1 (0.2)	1 (0.2)
Hypertensive crisis	3 (0.7)	2 (0.5)	2 (0.5)
Malignant hypertension	1 (0.2)	1 (0.2)	1 (0.2)
Aortic aneurysm	1 (0.2)	1 (0.2)	0

	Total Droxidopa (N=422)		
System Organ Class Preferred Term	**TEAEs n [%]**	**SAEs n [%]**	**TEAEs Leading to Discontinuation n [%]**
General Disorders and Administration Site Conditions	**7 (1.7)**	**3 (0.7)**	**1 (0.2)**
Sudden cardiac death	1 (0.2)	1 (0.2)	0
Chest pain	4 (0.9)	1 (0.2)	1 (0.2)
Chest discomfort	3 (0.7)	1 (0.2)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of an AE during the same treatment phase, the patient was included only once in the respective patient count. Adverse events were coded using MedDRA version 10.1.

7.5.4 Cerebrovascular TEAEs

Due to the mechanism of action of droxidopa, cerebrovascular TEAEs are of particular interest. There were no cerebrovascular TEAEs reported during Studies 301/302 or Study 306. In the open-label long-term extension studies, 3 patients (0.7%) reported an SAE of transient ischemic attack, 2 patients (0.5%) reported an SAE of cerebral infarction, and 1 patient (0.2%) reported an SAE of cerebrovascular accident.

Of the 3 SAEs of transient ischemic attack, the Investigators assessed 2 of these events as unlikely related to study drug and the third event as not related to study drug. Of the 2 SAEs of cerebral infarction, 1 was assessed by the Investigator as being possibly related to study drug while the other event was assessed as unrelated to study drug. The SAE of cerebrovascular accident was assessed by the Investigator as being possibly related to study drug. Additional information for these and all SAEs is provided in Appendix 5 (Section 10.5).

7.6 Clinical Laboratory Evaluations

7.6.1 Short-Term Placebo-Controlled Studies

Mean laboratory parameters were within normal limits in both the placebo and droxidopa groups and there were no clinically meaningful trends from Baseline to End of Study in any of the parameters during the RCT phase of Studies 301/302 and Study 306. There were some isolated and generally comparable shifts from normal at Baseline to out of range (low or high) in individual laboratory parameters in both the droxidopa and placebo groups; none of these were considered to be clinically meaningful. Across the short-term placebo-controlled studies, a low percentage of subjects reported laboratory-related TEAEs; all events but 1 were mild or moderate in severity (a TEAE of hematuria was reported as being severe in Study 306, but was considered by the Investigator to be unrelated to study drug).

7.6.2 Long-Term Extension Study Grouping

Mean and median values showed no evidence of a treatment effect on any laboratory parameter in the long-term extension study grouping. Mean and median laboratory parameters were generally within normal limits for all parameters at each of the monthly visits in which there was a suitable numbers of patients for analysis (n≥30).

Table 7-24 shows data for laboratory parameters in which ≥10% of patients shifted from normal at Baseline to out of range (low or high). Shifts to increased blood urea nitrogen (BUN) and increased creatinine in >5% of patients were observed at the majority of study visits in the long-term extension study group; however, there was no clear temporal trend in these parameters when individual patient data were reviewed. The only parameter for which there was a shift of ≥10% of patients at the majority of study visits were shifts to low hematocrit and shifts to low red blood cells (RBCs).

Table 7-24 Long-term Extension Study Grouping: Shift Table of Laboratory Results for Shifts in ≥10% of Patients Relative to the Normal Range (Safety Set)

	Total Droxidopa (N=422) n (%)										
Baseline [1] to:	Month 1	Month 2[3]	Month 3	End of Randomization[3]	Month 6	Month 9	Month 12	Month 18	Month 24	Month 30	Month 36
Abs. Lymphocyte count (x10/L)											
n[2]	363	70	324	71	275	207	177	96	39	15	11
Normal to Low	20 (5.5)	4 (5.7)	27 (8.3)	9 (12.7)	16 (5.8)	16 (7.7)	19 (10.7)	7 (7.3)	2 (5.1)	4 (26.7)	2 (18.2)
Normal to High	0	0	0	0	1 (0.4)	2 (1.0)	2 (1.1)	0	0	0	0
Abs. Neutrophil count (x10/L)											
n[2]	361	68	325	70	273	206	176	96	39	15	11
Normal to Low	3 (0.8)	1 (1.5)	4 (1.2)	1 (1.4)	2 (0.7)	1 (0.5)	2 (1.1)	0	0	0	0
Normal to High	8 (2.2)	1 (1.5)	8 (2.5)	3 (4.3)	5 (1.8)	4 (1.9)	7 (4.0)	1 (1.0)	5 (12.8)	0	0
BUN (mmol/L)											
n[2]	369	70	329	68	277	208	175	95	39	15	11
Normal to Low	0	0	1 (0.3)	0	0	0	0	0	0	0	0
Normal to High	17 (4.6)	5 (7.1)	15 (4.6)	8 (11.8)	19 (6.9)	18 (8.7)	12 (6.9)	8 (8.4)	3 (7.7)	1 (6.7)	1 (9.1)
CK (U/L)											
n[2]	368	69	328	67	277	207	175	95	39	15	11
Normal to Low	0	0	0	0	0	0	0	0	0	0	0
Normal to High	23 (6.3)	3 (4.3)	18 (5.5)	2 (3.0)	15 (5.4)	9 (4.3)	5 (2.9)	7 (7.4)	3 (7.7)	2 (13.3)	1 (9.1)
CK-MB[4] (µg/L)											
n[2]	75	11	74	12	62	43	38	28	10	6	4
Normal to Low	0	0	0	0	0	0	0	0	0	0	0
Normal to High	6 (8.0)	2 (18.2)	3 (4.1)	0	5 (8.1)	0	3 (7.9)	3 (10.7)	1 (10.0)	0	0
Creatinine (µmol/L)											
n[2]	369	71	328	69	276	207	176	95	39	15	11
Normal to Low	1 (0.3)	2 (2.8)	1 (0.3)	1 (1.4)	1 (0.4)	0	1 (0.6)	1 (1.1)	0	0	0
Normal to High	28 (7.6)	9 (12.7)	21 (6.4)	8 (11.6)	16 (5.8)	19 (9.2)	16 (9.1)	8 (8.4)	6 (15.4)	0	2 (18.2)
Glucose (random) (mmol/L)											
n[2]	358	70	314	67	270	198	167	87	34	13	10
Normal to Low	2 (0.6)	0	1 (0.3)	0	1 (0.4)	3 (1.5)	1 (0.6)	1 (1.1)	0	0	0
Normal to High	25 (7.0)	8 (11.4)	26 (8.3)	5 (7.5)	25 (9.3)	18 (9.1)	16 (9.6)	7 (8.0)	2 (5.9)	2 (15.4)	1 (10.0)

	Total Droxidopa (N=422) n (%)										
Baseline [1] to:	**Month 1**	**Month 2[3]**	**Month 3**	**End of Randomization[3]**	**Month 6**	**Month 9**	**Month 12**	**Month 18**	**Month 24**	**Month 30**	**Month 36**
Hematocrit (L/L)											
n[2]	372	74	330	73	278	210	178	97	39	15	11
Normal to Low	66 (17.7)	6 (8.1)	50 (15.2)	5 (6.8)	49 (17.6)	45 (21.4)	31 (17.4)	16 (16.5)	8 (20.5)	4 (26.7)	2 (18.2)
Normal to High	1 (0.3)	0	0	0	0	0	1 (0.6)	0	0	0	1 (9.1)
Hemoglobin (g/L)											
n[2]	369	72	329	70	276	209	177	97	39	15	11
Normal to Low	25 (6.8)	5 (6.9)	18 (5.5)	7 (10.0)	22 (8.0)	25 (12.0)	15 (8.5)	7 (7.2)	1 (2.6)	0	1 (9.1)
Normal to High	2 (0.5)	0	0	0	0	0	1 (0.6)	1 (1.0)	0	0	0
pH											
n[2]	230	68	209	65	181	131	108	53	37	15	10
Normal to Low	6 (2.6)	7 (10.3)	8 (3.8)	4 (6.2)	16 (8.8)	8 (6.1)	6 (5.6)	2 (3.8)	3 (8.1)	0	2 (20.0)
Normal to High	9 (3.9)	2 (2.9)	7 (3.3)	4 (6.2)	4 (2.2)	2 (1.5)	5 (4.6)	1 (1.9)	0	1 (6.7)	0
RBC (x10/L)											
n[2]	371	73	329	73	277	210	179	97	39	15	11
Normal to Low	58 (15.6)	5 (6.8)	44 (13.4)	6 (8.2)	42 (15.2)	36 (17.1)	24 (13.4)	18 (18.6)	8 (20.5)	3 (20.0)	2 (18.2)
Normal to High	3 (0.8)	0	3 (0.9)	0	2 (0.7)	0	0	0	0	0	1 (9.1)
WBC (x10/L)											
n[2]	366	69	327	71	277	210	177	97	39	15	11
Normal to Low	22 (6.0)	7 (10.1)	19 (5.8)	8 (11.3)	14 (5.1)	14 (6.7)	15 (8.5)	5 (5.2)	2 (5.1)	0	0
Normal to High	7 (1.9)	1 (1.4)	6 (1.8)	1 (1.4)	4 (1.4)	0	5 (2.8)	1 (1.0)	1 (2.6)	0	0

BUN=blood urea nitrogen; CK=creatine phosphokinase; CRF=case report form; MB=myocardial band; RBC=red blood cell; WBC=white blood cell.

Note: For Study 304, visit windows were assigned based on the study day for Month 12 and Final Study Visits. Data from all other visits were summarized as recorded in the CRF.

1 For Protocol 303, Baseline is the last non-missing value prior to the first dose of study treatment as part of Protocol 301 or 302. For Protocol 304, baseline is the last non-missing value prior to the first dose of study treatment as part of Protocol 304.

2 All n's are calculated by subtracting the number of patients with missing values from the total number of patients.

3 Values at End of Randomization and Month 2 are for Study 303 patients only.

4 Percent calculated based on events per total patients with a CK-MB value.

In Study 303 a total of 21 of 102 (20.6%) patients experienced 59 TEAEs related to abnormal laboratory parameters. All of the laboratory TEAEs were mild or moderate in severity. The majority (72.9%) of the 59 TEAEs associated with abnormal laboratory parameters were considered to be not related or unlikely related to study drug.

In Study 304, 52 of 350 patients (14.9%) reported a total of 158 TEAEs related to abnormal laboratory parameters. All of these TEAEs were mild or moderate in intensity except for a severe unlikely related TEAE of hypoglycemia, a severe unrelated TEAE of anemia, and an unlikely related severe TEAE of blood potassium decreased. The majority (88.0%) of the TEAEs associated with abnormal laboratory parameters were considered to be not related or unlikely related to study drug. The only event considered to be serious was a moderate TEAE of hyponatremia.

7.7 Other Safety Data

Droxidopa had no meaningful effect on HR or body weight across studies. Droxidopa was not associated with electrocardiogram (ECG) abnormalities. Study 102, a dedicated, thorough QTc study, concluded there was no signal of an effect of droxidopa on cardiac repolarization, HR, atrioventricular conduction, or cardiac depolarization (data not shown).

Safety data from the DSP-sponsored clinical studies conducted in Europe as well as from additional indications are consistent with the safety profile of droxidopa from the Sponsor's clinical development program.

Droxidopa was approved in Japan in 1989 for the treatment of OH, syncope, and dizziness on standing up in FAP and Shy-Drager Syndrome (i.e., MSA), and for the treatment of freezing phenomenon and dizziness on standing up in PD. In 2000, this approval was expanded to include the alleviation of vertigo, staggering, dizziness on standing up, lassitude, and weakness in hemodialysis patients with OH. An estimated 46,000 patients per year receive droxidopa in Japan, resulting in >1 million patient years of exposure.

During a 10-year period from 1989-1999, post-marketing data were collected in Japan following the marketing approval of droxidopa through the conduct of post-marketing surveys and through collection of spontaneous AEs reported by health care providers. During this time period, data were obtained from 1856 patients, 502 of whom had received droxidopa for >1 year. No specific AEs were reported that were attributed to the long-term use of droxidopa. Cases of neuroleptic malignant syndrome (NMS), a documented AE that occurs in patients with PD abruptly stopping L-DOPA and other anti-Parkinson's drugs, were reported during this 10-year period; however, following an external expert review of each of these cases, it was concluded that droxidopa was unrelated to these events of NMS. Furthermore, none of the cases were associated with the dose escalation or withdrawal of droxidopa.

7.8 Dose Recommended for Proposed Clinical Use

The clinical presentation of symptomatic nOH is heterogeneous. Patients with nOH vary with respect to primary diagnosis, age of onset, concomitant medication use, disease severity, and disease progression. Furthermore, patients with nOH may present with varying risk factors

associated with supine hypertension. Consequently, optimal dosing for therapeutic agents for the treatment of nOH is best done on an individual basis, and the Sponsor is recommending the following for the "Dosage and Administration" section of the proposed Prescribing Information:

> The recommended starting dose of NORTHERA is 100 mg, taken orally three times daily (TID): upon arising in the morning; midday; and late afternoon at least 3 to 4 hours prior to bedtime (to reduce the potential for supine hypertension during sleep). Patients should take NORTHERA consistently either with food or without food. Dose optimization should be based on a patient's symptomatic response and clinical condition. The dose may be increased in increments of 100 mg TID every 24 to 48 hours up to a maximum dose of 600 mg TID (i.e., a maximum total daily dose of 1800 mg).
>
> Dose optimization should be based on a patient's symptomatic response after at least one full day on therapy. During clinical trials, dose optimization was usually conducted on a daily basis and completed within a 10 day period. Supine BP should be monitored regularly and more frequently when changing dose. The dose of NORTHERA should be reduced or administration stopped if supine BP increases excessively. The last dose should be taken at least 3-4 hours before bedtime.
>
> Patients who miss a dose of NORTHERA should take their next scheduled dose. Patients should not take more than the prescribed total daily amount of NORTHERA in any 24-hour period.

7.9 Conclusions on Safety

There are no new safety issues or findings of concern that have arisen from the expanded safety database since filing the original NDA and the Cardiovascular and Renal Advisory Committee Meeting held in 2012. The FDA identified no safety issues of concern in the CR Letter (March 2012). Importantly, the addition of Study 306, which includes 8 to 10 weeks of placebo-controlled comparative safety data and comparative safety data during dose titration, has greatly expanded the safety database from the original NDA for this orphan indication. The incidences of SAEs, BP-related TEAEs, TEAEs related to cardiovascular events, and cerebrovascular TEAEs were low and consistent across both the short-term placebo-controlled and long-term extension studies. The most common TEAE terms and rates were also consistent across the short-term placebo-controlled and long-term extension studies.

Overall, droxidopa therapy was well tolerated at all doses. Droxidopa treatment was associated with a small increase in the incidence of headache, dizziness, nausea, hypertension, and fatigue. Most TEAEs were mild to moderate in severity, and events were generally considered by Investigators to be unlikely or not related to study drug. Results from DSP-sponsored trials as well as post-marketing surveys also revealed that droxidopa is associated with a low incidence of TEAEs and SAEs, and no specific TEAEs, including NMS, were reported that were attributed to the long-term use of droxidopa.

8. BENEFITS AND RISKS

Summary of Benefits

The totality of data from the Sponsor's clinical development program, including those collected during 2 randomized, placebo-controlled induction design studies and multiple other supportive studies demonstrates consistent short-term benefits for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

Short-term effectiveness was demonstrated across a range of symptoms and pharmacodynamic measures including improvements in dizziness/lightheadedness/syncopal symptoms, a core symptom of nOH; increases in standing BP; reduction of falls and fall-related injuries (Study 306); and global improvements as assessed by clinicians (CGI-S and CGI-I).

The apparent reduction in falls is an objective measure that provides independent substantiation and supportive evidence of the clinical benefits of droxidopa. This benefit was corroborated by a lower number of fall-related injuries, including potentially debilitating injuries, in patients treated with droxidopa compared with those treated with placebo.

Results from long-term studies (Study 303 following up to 12 months of open-label treatment and Study 306 following up to 2 months of double-blind treatment) provide evidence that the benefits of droxidopa on both symptoms and standing BP are durable. In addition to these current long-term results, Chelsea plans to conduct a randomized-controlled post-marketing study to confirm the findings generated thus far from the droxidopa development program.

Each study is associated with some limitations. Site effects diminish the persuasiveness of Study 301. To address this, the Sponsor performed a careful review of data at the site level, along with regional sensitivity analyses. Regardless of the potential site effects, the data from Study 301 conclusively demonstrate the efficacy of droxidopa. The interpretation of Study 306B is limited by missing data for patients dropping out during titration. However, multiple sensitivity analyses coupled with conclusions drawn from an evaluation of the reasons for patient discontinuation support the conclusions that Study 306B provides substantial evidence of the short-term effectiveness of droxidopa. Studies 302 and 303 were likely underpowered to show a treatment effect and may have been confounded by a carry-over effect.

The collective data from the Sponsor's clinical development program demonstrate that droxidopa is effective for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

Summary of Risks

The droxidopa safety database generated by the Sponsor and DSP is large relative to the population of patients diagnosed with this Orphan Drug condition, and demonstrates that droxidopa is safe and well tolerated. The overall incidence of TEAEs was similar between droxidopa and placebo in placebo-controlled studies. Droxidopa treatment was associated with a small increase in the incidence of headaches, dizziness, nausea, and hypertension. Most TEAEs were mild to moderate in severity, and events were generally considered by the Investigators to

be unlikely or not related to study drug. Longer-term studies were not associated with a change in the incidence or types of TEAEs observed in the short-term trials.

Droxidopa modestly increases the incidence of supine hypertension and BP-related TEAEs in this population and not to severe levels in most instances. However, the overall incidence of cardiovascular-related TEAEs experienced by patients treated with droxidopa was low. A dedicated 24-hour ambulatory BP monitoring study showed no difference in the increase on drug versus off drug in nocturnal (supine) compared with diurnal BPs. The risk of supine hypertension can be addressed with appropriate patient selection, BP monitoring, and labeling. The results of a thorough clinical QT/QTc study indicate that droxidopa has no effect on cardiac repolarization or other atrial or ventricular conduction parameters.

Despite the low incidence of observed cardiovascular-related TEAEs, an independent review of the cardiovascular and cerebrovascular safety data was performed. This review confirmed the clinical diagnoses of the serious cardiovascular events and reported rates in the droxidopa studies were not in excess of what would be expected for the background rates in patients with nOH.

To maximize the benefits and minimize potential risks of droxidopa therapy given the heterogeneity of the patient population and variable risk factors associated with symptomatic nOH, the Sponsor proposes that droxidopa be administered using an individualized dose optimization strategy.

Conclusions

nOH is a debilitating illness with a significant unmet medical need. Droxidopa is the only agent to have demonstrated, in adequate and well-controlled trials, improvements in the signs and symptoms of nOH. Droxidopa is generally safe and well tolerated. There is a small increase in the incidence of supine hypertension associated with droxidopa therapy which is both predictable and manageable. The totality of data from the Sponsor's clinical development program, including those collected during 2 positive, randomized, placebo-controlled trials, coupled with those from European and Japanese studies of droxidopa, demonstrate that droxidopa is safe and effective for the treatment of symptomatic nOH in patients with primary autonomic failure (PD, MSA, and PAF), DβH Deficiency, and NDAN.

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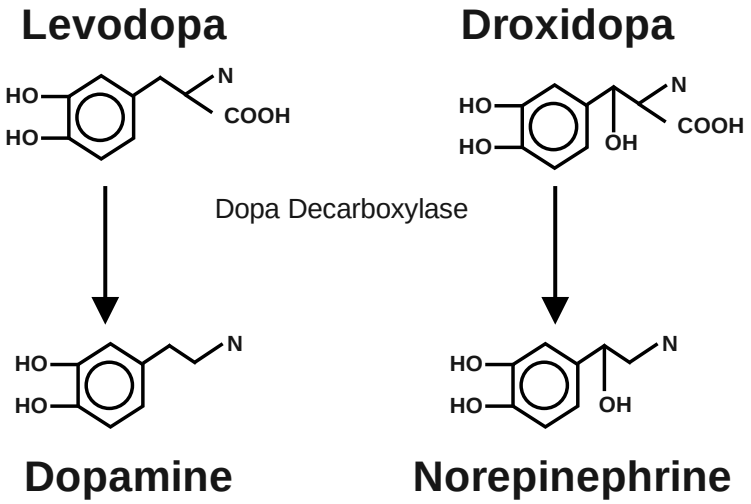
10. APPENDICES

10.1 Appendix 1: Overview of Clinical Pharmacology Profile of Droxidopa

10.1.1 Pharmacokinetics

Droxidopa is an orally bioavailable, synthetic catecholamine acid pro-drug that is converted to NE through a single step of decarboxylation by the endogenous enzyme DOPA decarboxylase, an enzyme found in many tissues including autonomic nerve terminals; DOPA decarboxylase is the same enzyme responsible for the conversion of levodopa to dopamine (Figure 10-1). Droxidopa is not known to have intrinsic biological activities on its own, but its active metabolite NE binds to both alpha- and beta-adrenergic receptors. Droxidopa produces mild increases in BP in normal animals given high doses of the drug and improvement in orthostatic hypotension seen in rats chemically depleted of NE.

Figure 10-1 Metabolism of Droxidopa to Norepinephrine



10.1.2 Metabolism

The primary metabolite of droxidopa in humans and animals in tissue, serum, and urine is 3-OM-DOPS. Droxidopa may be initially converted to 3-OM-DOPS by COMT; to NE by DOPA decarboxylase; or to protocatechualdehyde by DOPS aldolase. These primary metabolites are further metabolized as follows: 3-OM-DOPS is converted to the secondary metabolite vanillic acid (VA); and NE is converted to the secondary metabolite 3-methoxy-4-hydroxy-phenylglycol (HMPG) by COMT and monoamine oxidase (MAO), which may then be converted to the tertiary metabolite dihydroxyphenylglycol (DHPG) by aldehyde/aldose reductase. Protocatechualdehyde appears to be highly reactive and is rapidly converted to protocatechuic acid (PA) by an aldehyde dehydrogenase or, to a lesser degree, 3,4-dihydroxytoluene (HC) via reductive metabolism.

When assessed in *in vitro* studies, droxidopa neither inhibited nor induced the tested cytochrome P450 isozymes (CYP 450 isozymes tested for inhibition: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4; CYP 450 isozymes tested for induction: CYP1A2, 2B6 and 3A4/5).

Therefore, droxidopa has a low potential for cytochrome P450 metabolically-mediated drug-drug interactions.

10.1.3 Absorption, Distribution, and Elimination

After oral administration to patients or young and elderly, healthy, male and female volunteers, droxidopa is rapidly absorbed. Droxidopa plasma concentrations peak at about 2 hours (range of 1 to 4 hours) and thereafter decline monoexponentially with a half-life of about 2 to 3 hours (Goldstein et al, 2004). Droxidopa is known to cross the blood-brain barrier. Droxidopa has an apparent volume of distribution at steady-state of 200 L based on a population PK analysis of data from Phase 3 Study 302.

Droxidopa exhibits concentration-dependent serum protein binding over the range of concentrations expected to be encountered therapeutically, decreasing from 75.4% ± 0.26% at 100 ng/mL (0.1 mcg/mL) to 26.2% ± 1.03% at 10,000 ng/mL. Given the low to modest serum protein binding of droxidopa, no protein binding-mediated drug-drug interactions would be expected. The serum protein binding of the droxidopa primary metabolite, 3-OM-DOPS, is minimal (~1%). Droxidopa was excreted into the milk of lactating rats receiving an oral radiolabeled dose of droxidopa.

Droxidopa and 3-OM-DOPS, its primary metabolite, were found in human urine after single oral doses droxidopa to young healthy male volunteers. Based on radiolabeled mass balance studies in mice, rats, dogs and monkeys, the predominant route of excretion of droxidopa and related metabolic products is via the urine, ranging from 60% to 72% among species. Fecal excretion is a minor route, ranging from 9% to 20% among species. In animals, the renal clearance of radioactive label accounted for up to approximately 75% of total radiolabeled dose, including the parent drug (15%) and the major metabolites (3-OM-DOPS [6%-15%], protocatechualdehyde [10%-20%], and VA [2%-11%]).

10.1.4 Population Pharmacokinetics

The Chelsea clinical pharmacology program has been conducted in young and elderly, healthy, male and female volunteers as well as patients with nOH, the latter being a population that is representative of the intended general patient population with regard to concomitant medication use and diseases typical of the elderly. The PK properties of droxidopa were characterized in Chelsea-sponsored clinical studies after single oral doses of 300 mg to 2000 mg droxidopa in 76 healthy volunteers (Study 101 and Study 102) and after multiple oral dosing of 100 mg to 600 mg droxidopa TID in 89 patients with nOH in Study 302. Supportive PK data were also obtained from other studies.

In Study 302, relationships between covariates (dose, age, gender, race, weight, height, BMI, country, hepatic function ALT, AST, alkaline phosphatase, total bilirubin], renal function [creatinine clearance], and concomitant medications) and *post-hoc* (individual) parameters were evaluated and incorporated into the population PK model. The major findings include:

- Linear but less than dose-proportional increases in exposure (C_{max} and AUC) are seen upon administration of increasing single oral doses of droxidopa. The relative bioavailability of

droxidopa decreases significantly upon administration of single oral doses of 900 mg or greater.

- Absorption was delayed by increased body weight (each kg increased mean absorption time by 1.4%) and with each 100 mg increase in dose of droxidopa (mean absorption time increased by 9.3%). While time to maximum plasma concentration (T_{max}) and C_{max} were influenced by each 100 mg increase in dose of droxidopa, the relative bioavailability of droxidopa (as assessed by apparent clearance) was independent of dose between 100 mg to 600 mg when administered TID. Thus, the rate of absorption but not the extent of absorption was influenced by increased body weight and each 100 mg increase in dose.

- Exposure to droxidopa was not affected by body size (weight, height, BMI) or gender.

- Hepatic function did not influence exposure to droxidopa.

- Renal function was correlated with increased exposure, but changes in creatinine clearance, as expected, appeared to be a function of age in this study.

- Increasing age was associated with an increase in exposure (decreased clearance of ~0.8% per year of age) for droxidopa. Age correlated more strongly to exposure than did renal function; once age was entered into the model, there no longer was a relationship between exposure and renal function.

- Concurrent administration of L-DOPA (in combination with a DDC-I) was associated with an approximate 2-fold increase in droxidopa exposure (AUC) or a 53% decrease in the apparent clearance of droxidopa.

10.1.5 Food Effect

A food effect study was conducted (Study 101) to evaluate the effects of a high-fat meal on the PK profile of droxidopa in healthy, elderly subjects. This study was a randomized, open-label, three-period, three-sequence randomized crossover study in 24 healthy, elderly (aged 65 years and older), male or female subjects under fasting and fed conditions. All subjects were to receive one administration of 300 mg of droxidopa (3 × 100 mg capsules) under fasted and fed conditions. It was observed that food decreased the rate and extent of droxidopa absorption. A high fat/high caloric meal resulted in a delay in the droxidopa T_{max} from 2 hours to 4 hours, and systemic exposure as assessed by C_{max} and AUC values were each reduced by 35% and 20%, respectively. The terminal half-life of droxidopa was approximately 2.6 hours and was consistent between fasted and fed.

10.1.6 Summary of Pharmacokinetic Issues

Administration of droxidopa with a meal is not likely to affect the safety profile of droxidopa as the systemic exposure to droxidopa will be reduced when taken in the fed compared to the fasting state. However, it is recommended that droxidopa be taken at the same time of day TID either with or without meals consistently each day. This approach will lead to a more consistent daily systemic exposure to droxidopa.

Given the prominence of the renal route of excretion, there is a potential for renal impairment to increase exposure to droxidopa and/or its metabolites. Renal function decreases as a function of increasing age and the findings of the aforementioned population PK analysis showed that increasing age was associated with an increase in exposure to droxidopa. Droxidopa has not yet been studied in subjects with severe renal dysfunction (glomerular filtration rate [GFR] <20 mL/min); however, as agreed upon with the FDA, Chelsea intends to conduct a post-marketing study in patients with varying degrees of renal impairment. Of note, patients with mild or moderate renal impairment (GFR ≥20 mL/min) were included in the droxidopa clinical trials without increases in associated adverse events (data not shown).

In the Phase 3 clinical trials, droxidopa could be concomitantly administered with any PD medications. Dopamine agonists, amantadine derivatives, MAO-B inhibitors, and COMT inhibitors did not appear to affect the clearance of droxidopa and, therefore, droxidopa dose adjustments are not required when taken with these medications. Patients taking droxidopa with L-DOPA/DOPA-decarboxylase inhibitor combination drugs had a decreased clearance of droxidopa, with an associated 2-fold increase in exposure based on AUC. However, the decreased clearance of droxidopa was not associated with a significant difference in the determination of an optimal treatment dose of droxidopa. Nevertheless, initiation of therapy with or changes in the dose or administration of L-DOPA/DOPA-decarboxylase inhibitor combination drugs may require dose adjustments of droxidopa.

10.1.7 Pharmacodynamics

Given the extensive distribution of the DOPA-decarboxylase enzyme, the conversion of droxidopa to NE can occur peripherally and/or centrally. The pressor effects of droxidopa were demonstrated in a number of *in vivo* models of hypotension in several different animal species following oral administration. Additionally, when employing inhibitors of the metabolic pathway for droxidopa, it was determined that the specific effects of droxidopa were mediated by NE and not droxidopa or its primary metabolite, 3-OM-DOPS.

The *in vivo* effects of droxidopa on BP and HR were blocked by inhibitors of DOPA-decarboxylase (e.g., benserazide), suggesting that these effects were due to the formation of NE and not intrinsic to droxidopa itself. Furthermore, while other major metabolites of droxidopa (3-OM-DOPS, protocatechualdehyde, and VA [a metabolite of 3-OM-DOPS]) may have some vasomotor activity, their contribution is considered minor as they do not appear to significantly influence the pharmacodynamic effect of droxidopa. Theoretically, the co-administration of droxidopa with inhibitors of DOPA-decarboxylase and the catecholamine pathway enzymes, COMT and MAO-B, could result in increased systemic exposure to droxidopa.

Norepinephrine increases BP by inducing peripheral arterial and venous vasoconstriction, and has known effects in the central nervous system. In mouse models of PD, droxidopa was demonstrated to cross the blood-brain barrier and ameliorate the decreased function of central noradrenergic neurons as well as to antagonize behavioral changes resulting from this decreased function (hypoactivity, hypothermia and ptosis;). Droxidopa has been shown to be taken up into human brain synaptosomes by an active transport system commonly used by L-amino acids. Pharmacology studies have shown that droxidopa increases the content of both NE and its main

metabolite, methoxy-4-hydroxyphenylglycol (MHPG), in the brains of normal animals. Droxidopa also restores or replenishes NE content in the brain of NE-depleted animals, demonstrating that it acts as a NE precursor in the central nervous system. In addition to its function as an NE precursor, droxidopa promoted the release of NE from the nerve endings in experiments using brain synaptosomes and slices (Nishino et al, 1987).

The exact mechanism of action of by which droxidopa produces clinical effects is unknown. In humans, droxidopa induces relatively small transient rises (<2 ng/mL) in plasma NE. The relative contribution of droxidopa to NE plasma concentrations depends on the endogenous production of NE, which likely fluctuates markedly in patients with primary autonomic failure (PD, MSA and PAF), DβH Deficiency or NDAN and symptomatic nOH compared with fluctuations seen in young healthy male volunteers.

The pharmacodynamic effects of droxidopa on BP generally mirror the PK profile of droxidopa. Peak BP effects occurred at approximately 2 to 3 hours post dose in Study 101 and Study 102. The effect of acute doses of droxidopa on BP generally dissipated by approximately 6 hours post-dose. Given the time course of the effect of droxidopa on BP relative to an oral dose and the potential for increased BP while in the supine position, it is recommended that the last daily dose of droxidopa be taken at least 3 to 4 hours before bedtime.

There was no effect of droxidopa on cardiac repolarization after a single oral dose of 600 mg (therapeutic dose) or 2000 mg (supratherapeutic dose) in 52 healthy subjects participating in the thorough QT/QTc study (Study 102). Based on the primary endpoint, placebo-corrected change from baseline in QTcI (ΔΔQTcI), there was no significant relationship between ΔΔQTcI and plasma droxidopa concentration.

Pharmacodynamic drug interactions indicate that L-DOPA could potentially increase the plasma levels of droxidopa and NE possibly by competing for binding to metabolizing enzymes, and that drugs such as amezimium, which have hypertensive properties and act through binding to adrenergic receptors or by altering the metabolism of catecholamines, could potentially affect the action of droxidopa. Additionally, caution should be used in administering droxidopa in combination with drugs that increase BP, such as NE (intravenous [IV]), ephedrine, midodrine, and sumatriptan-like drugs, as these drugs have not been studied in combination with droxidopa.

10.2 Appendix 2: Chelsea-sponsored Clinical Studies

A description of Chelsea's clinical trials are summarized in the tables below. A full description of the design of Studies 301, 306B, 302, and 303 are provided in Sections 6.1.1, 6.1.2, 6.1.4, 6.2.1, respectively.

Brief descriptions of the designs of Studies 304, 305, 101, 102, and 104 are provided within this Appendix.

10.2.1 Study 301

Table 10-1 Description of Study 301

Study Design	Number of Patients/Study Population	Study Objectives	Primary Efficacy Endpoint and Safety Endpoints	Primary Efficacy and Safety Results
Study 301 was a Phase 3, multi-center, multi-national, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose-titration prior to a 7-day washout period, followed by a 7-day double-blind randomized treatment period (Figure 6-1). Doses of droxidopa ranged from 100 to 600 mg TID.	N=263 n=84 randomized to droxidopa n=84 randomized to placebo n=95 not randomized Note: 6 patients were randomized but did not receive double-blind study medication; therefore, they were excluded from the FAS and the Safety Set. Symptomatic nOH in patients with primary autonomic failure, DβH Deficiency, or NDAN	Primary: relative mean change in OHQ composite score 7 days following randomization to treatment with droxidopa or placebo Secondary: • symptom and activity measurements using the OHSA and OHDAS individual and composite scores, the two subcomponents of the OHQ; • clinician-rated and patient-rated CGI-S and CGI-I scales; • changes in SBP and DBP measurements 3 minutes post-standing; • Safety of droxidopa as measured by the occurrence of treatment emergent AEs and evaluations of BP, HR, ECG, and laboratory findings.	Efficacy: the mean change in the OHQ composite score from Randomization to End of Study Safety: AE monitoring Clinical laboratory parameters Vital signs ECG Concomitant medications	Efficacy: The mean changes from Randomization to End of Study (i.e., Week 1) in the OHQ composite score (the primary endpoint) and OHSA Item 1 (a key secondary endpoint) showed statistically significant benefits favoring droxidopa (OHQ composite score: 0.90 units favoring droxidopa [p=0.003]; OHSA Item 1: 1.3 units favoring droxidopa [p<0.001]). In addition, a statistically significant improvement in standing SBP was observed after 1 week of treatment (7.3 mmHg favoring droxidopa [p<0.001]). Safety: •The most common AEs reported in the droxidopa vs. the placebo group during the RCT Phase were headache (7.4% vs. 0), dizziness (3.7% vs. 1.2%), nausea (2.5% vs. 0), and fatigue (2.5% for each). •No deaths were reported during the study. • Thirteen patients (4.9%) reported AEs during Titration that led to discontinuation from the study; none were reported during the RCT Phase. • No SAEs were reported by droxidopa-treated patients during the RCT.

AE=adverse event; BP=blood pressure; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; CV=cardiovascular; DBP=diastolic blood pressure; DβH=dopamine beta hydroxylase; DDC-I=3,4-dihydroxyphenylalanine decarboxylase inhibitor; ECG=electrocardiogram; FAS=Full Analysis Set; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; OHDAS=Orthostatic Hypotension Daily Activities Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SAE=serious adverse event; SBP=systolic blood pressure; SD=standard deviation; TID=three times daily.

10.2.2 Study 306

Table 10-2 Description of Study 306B

Study Design	Number of Patients/Study Population	Study Objectives	Primary Efficacy Endpoints and Safety Endpoints	Primary Efficacy and Safety Results
Study 306B was a Phase 3, multi-center, placebo-controlled, parallel-group, induction design, double-blind study with an initial double-blind dose-titration, followed by a double-blind 8-week treatment period (Figure 6-14). Doses of droxidopa ranged from 100 to 600 mg TID.	N=174 n=89 randomized to droxidopa n=85 randomized to placebo Note: 3 patients were randomized but never treated and therefore were excluded from the FAS and the Safety Set. Symptomatic nOH in patients with PD	Efficacy: Primary: improvements in OHSA Item 1, from Baseline to Visit 4 (Week 1) Secondary: • improvements in OHSA Item 1 across study visits • difference in patient reported falls • change in symptom measurements (OHSA composite score and OHSA Items 1 to 6), and change in activity measurements (OHDAS composite score and OHDAS Items 1 to 4); • change in the clinician-recorded and patient-recorded CGI-S and CGI-I scales; • standing time (change across study visits) • standing BP (across study visits) Safety (Study 306AB Composite): Safety and tolerability of droxidopa by occurrence of TEAEs and changes in BP, HR, MDS-UPDRS, PDQ-39, ECG, and laboratory measurements.	Efficacy: Mean change in OHSA Item 1 from Baseline to Week 1 (Visit 4). Safety (Study 306AB Composite): AE monitoring Clinical laboratory parameters Vital signs ECG MDS-UPDRS PDQ-39 Concomitant medications	Efficacy: The mean change from Baseline to Week 1 in OHSA Item 1 (the primary endpoint) showed statistically significant benefits favoring droxidopa (1.0 units favoring droxidopa [p=0.018]). While a treatment difference in favor of droxidopa was observed at Week 1 for the OHQ composite score (an exploratory endpoint in this study; 0.4 units), this difference was not statistically significant (p=0.115). A statistically significant improvement in standing SBP was observed after 1 week of treatment (5.7 mmHg favoring droxidopa [p=0.032]). Safety (Study 306AB Composite): • The most common AEs reported in the droxidopa vs. the placebo group were headache (13.2% vs. 7.4%), dizziness (9.6% vs. 4.6%), nausea (8.8% vs. 4.6%), hypertension (7.0% vs. 0.9%), and fatigue (7.0% vs. 5.6%). • No deaths were reported in Study 306. • Twelve patients (10.5%) in the droxidopa group and 5 patients (4.6%) in the placebo group reported a TEAE that resulted in study drug discontinuation. • Five patients (4.4%) in the droxidopa group reported a total of 9 SAEs, and 4 patients (3.7%) in the placebo group reported a total of 5 SAEs.

AE=adverse event; BP=blood pressure; CFB=change from Baseline; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; ECG=electrocardiogram; EOS=end of study; FAS=Full Analysis Set; HR=heart rate; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; nOH=Neurogenic Orthostatic Hypotension; OHDAS=Orthostatic Hypotension Daily Activities Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; PDQ-39=Parkinson's Disease Questionaire-39; SAE=serious adverse event; SBP=systolic blood pressure; SD=standard deviation; TEAE=treatment-emergent adverse event; TID=three times daily.

Table 10-3 Description of Study 306A (Interim Analysis Dataset)

Study Design	Number of Patients/Study Population	Study Objectives	Primary Efficacy Endpoints and Safety Endpoints	Primary Efficacy and Safety Results
Study 306A (Interim Analysis Dataset) was a was a Phase 3, multi-center, placebo-controlled, parallel-group, induction design double-blind study with an initial double-blind dose-titration, followed by a double-blind 8-week treatment period. Doses of droxidopa ranged from 100 to 600 mg TID.	N=51 n=24 randomized to droxidopa n=27 randomized to placebo Symptomatic nOH in patients with PD	Efficacy: Primary: change in symptom and activity measurements using OHQ composite score. Secondary: • difference in patient-reported falls • change in symptom measurements (OHSA composite score and OHSA Items 1 to 6), and change in activity measurements (OHDAS composite score and OHDAS Items 1 to 4); • change in the clinician-recorded and patient-recorded CGI-S and CGI-I scales; • standing time (change from Baseline to EOS) • standing BP (change from Baseline to the end of titration)	Efficacy: Mean change from Baseline to End of Study (Visit 7) in the OHQ composite score.	Efficacy: Greater numerical improvements (i.e., decreases) from Baseline in mean OHQ composite score were observed with droxidopa compared with placebo. As expected, since Study 306A was not intended to serve as a stand-alone trial, mean CFB in OHQ composite score at EOS was not significantly different between droxidopa and placebo (p=0.978). Greater numerical improvements from Baseline were also observed on OHSA Item 1 with droxidopa compared with placebo (-2.5 units vs. -1.6 units, respectively).

AE=adverse event; BP=blood pressure; CFB=change from Baseline; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; ECG=electrocardiogram; EOS=end of study; FAS=Full Analysis Set; HR=heart rate; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating Scale; nOH=Neurogenic Orthostatic Hypotension; OHDAS=Orthostatic Hypotension Daily Activities Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; PDQ-39=Parkinson's Disease Questionaire-39; SAE=serious adverse event; SBP=systolic blood pressure; SD=standard deviation; TEAE=treatment-emergent adverse event; TID=three times daily.

10.2.3 Study 302

Table 10-4 Description of Supportive Study 302

Study Design	Number of Patients/Study Population	Study Objectives	Primary Efficacy Endpoint and Safety Endpoints	Efficacy and Safety Results
Study 302 was a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, parallel-group, withdrawal-design study with an initial open-label dose titration prior to a 7-day open-label treatment period, followed by a 14-day double-blind randomized-withdrawal period (Figure 6-31). Doses of droxidopa ranged from 100 to 600 mg TID.	N=181 n=50 randomized to droxidopa n=51 randomized to placebo n=80 not randomized Symptomatic nOH in patients with primary autonomic failure, DβH Deficiency, and NDAN	Primary: relative change in mean score of Item 1 of the OHSA 14 days following randomization to continued therapy with droxidopa or placebo. Secondary: • symptom and activity measurements using the composite scores of OHSA and OHDAS, the two subcomponents of the OHQ • clinician-rated and patient-rated CGI-S and CGI-I scales • changes in SBP and DBP measurements 3 minutes post-standing • Safety of droxidopa as measured by the occurrence of treatment emergent AEs and evaluations of BP, HR, ECG, and laboratory findings. Pharmacometric: development of a population pharmacokinetic and pharmacodynamic model within the target population.	Efficacy: the mean change in the score of Item 1 of the OHSA from Randomization to End of Study Safety: AE monitoring Clinical laboratory parameters Vital signs ECG Concomitant medications	Efficacy: While failing on the primary endpoint (mean change from Randomization to End of Study on OHSA Item 1; p=0.509), Study 302 provided supportive evidence to the results from Studies 301 and 306B and demonstrated the efficacy of droxidopa across a range of symptomatic and functional outcomes. For example, similar to the results from Study 301, based on a *post-hoc* analysis the mean change from Randomization to End of Study (i.e., Week 2) in the OHQ composite score demonstrated benefits favoring droxidopa (1.11 units favoring droxidopa [p=0.026]). Safety: • The most common AEs reported in the droxidopa vs. the placebo group during the RCT Phase were headache (4.0% vs. 7.8%), dizziness (4.0% vs. 2.0%), fatigue (0 vs. 2.0%), and fall (2.0% vs. 11.8%). • No deaths were reported during the study. Two deaths occurred outside the study (1 during Screening, prior to receiving droxidopa, 1 was 11 days after discontinuing the study). Details on all deaths can be found in Section 7.4.2. • Thirteen (7.2%) patients reported AEs during Titration that led to discontinuation from the study; no droxidopa-treated patients and 2 (3.9%) placebo-treated patients reported AEs leading to discontinuation during the RCT Phase. • In the RCT, 1 (2.0%) patient treated with placebo reported SAEs (no SAEs were reported by droxidopa-treated patients).

AE=adverse event; BP=blood pressure; CGI-I=Clinical Global impressions-improvement; CGI-S=Clinical Global Impressions-Severity; DBP=diastolic blood pressure; DβH=dopamine beta hydroxylase; ECG=electrocardiogram; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; OHDAS=Orthostatic Hypotension Daily Activities Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; SAE=serious adverse event; SBP=systolic blood pressure; SD=standard deviation; TID=three times daily.

10.2.4 Study 303

Table 10-5 Description of Study 303

Study Design	Number of Patients/Study Population	Study Objectives	Primary Efficacy Endpoint and Safety Endpoints	Efficacy and Safety Results
Study 303 was Phase 3, multi-center, multi-national study with an initial 3-month open-label treatment period followed by a 14-day double-blind, placebo-controlled, randomized-withdrawal period, followed by open-label treatment for remaining study duration (Figure 6-40). Doses of droxidopa ranged from 100 to 600 mg TID.	N=103 Note: 1 patient was enrolled but was never dosed with study drug, and was therefore excluded from the FAS and the Safety Set. Symptomatic nOH in patients with primary autonomic failure, DβH Deficiency, or NDAN	Entire Open-Label Period Primary Objective • Long-term safety of droxidopa as measured by the occurrence of treatment-emergent AEs and specific evaluations of BP, HR, ECG, and laboratory findings. Secondary Objective • Long-term clinical efficacy of open-label droxidopa. First 3-Month Open-Label Treatment Period Followed by a Randomized-Withdrawal Period Primary Objective • Long-term clinical efficacy of droxidopa as measured by the relative mean change of the OHQ composite score Secondary Objectives • Clinical efficacy of droxidopa as measured by OHSA, OHDAS, CGI-S and CGI-I scales, BP during the OST. • Safety of droxidopa as measured by the occurrence of treatment emergent AEs and evaluations of BP, HR, ECG, and laboratory findings.	Efficacy: Entire Open-Label Period: • Mean change in OHQ composite score from Baseline. Randomized-withdrawal Period: • Mean change in OHQ composite score from Randomization to the end of the 2-week randomization period. Safety: AE monitoring Clinical laboratory parameters Vital signs ECG Concomitant medications	Efficacy: In Study 303, improvements in OHSA Item 1 [dizziness/lightheadedness]) and in standing SBP were consistent and durable with long term droxidopa treatment. Improvements observed at Week 1 in both OHSA Item 1 and standing SBP were consistently maintained out to Week 52. There were no statistically significant differences between treatment groups during the randomized-withdrawal period. Safety: • The most frequent AEs in all droxidopa-treated patients were fall (20.6%), urinary tract infection (17.6%), headache (13.7%), syncope (12.7%), back pain (10.8%), and dizziness (7.8%). • Five patients died during Study 303 (1 during the 3-month open-label period and 4 during the long-term follow-up period). The fatal event in 1 of these 5 patients (hypoxic encephalopathy occurring in a patient taking droxidopa 400 mg TID) was considered possibly related to study drug by the Investigator. • Overall, 26 (25.5%) patients treated with droxidopa experienced a total of 47 SAEs, including 12 (11.8%) patients during the 3-month open-label phase and 16 (21.6%) patients during the long-term follow-up period. • Sixteen (15.7%) patients experienced an AE leading to study discontinuation, including 9 (8.8%) patients during the 3-month open-label period and 7 (9.5%) patients during the long-term follow-up period. • The incidence of supine hypertension was consistently low throughout the course of the study and showed no trends over time.

AE=adverse event; BP=blood pressure; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; DBP=diastolic blood pressure; DβH=dopamine beta hydroxylase; ECG=electrocardiogram; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; OHDAS=Orthostatic Hypotension Daily Activities Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; OST=Orthostatic Standing Test; SAE=serious adverse event; SBP=systolic blood pressure; SD= standard deviation; TID=three times daily.

10.2.5 Study 304

Study 304 was a multi-center, open-label, long-term extension study for Studies 301, 303, and 306 which included an initial 3-month, open-label treatment period with study visits at 1 and 3 months, followed by further open-label treatment with visits every 3 months for the remaining study duration. An initial open-label dose titration was required for patients who had never completed an open-label dose titration with droxidopa in a Chelsea-sponsored nOH study. This study examined safety as measured by the occurrence of treatment-emergent adverse events (TEAEs) and specific evaluations of BP, HR, and laboratory findings across the study.

A total of 350 patients were enrolled into Study 304 and received at least 1 dose of droxidopa and, thus, are included in the Safety Set.

A tabular summary of the patient population characteristics, study objectives, endpoints, and results is presented in Table 10-6.

Table 10-6 Description of Study 304

Study Design	Number of Patients/Study Population	Study Objectives	Safety Endpoints	Safety Results
Study 304 was a Phase 3, multi-center, multi-national, open-label study to evaluate the long-term safety of droxidopa. Doses of droxidopa ranged from 100 to 600 mg TID.	N=350 Symptomatic nOH in patients with primary autonomic failure, DβH Deficiency, or NDAN	To evaluate the long-term safety of droxidopa as measured by the occurrence of TEAEs and specific evaluations of BP, HR, and laboratory findings across the study	AE monitoring Clinical laboratory parameters Vital signs ECG Concomitant medications	• The most frequent AEs were fall (23.4%), urinary tract infection (13.4%), headache and syncope (12.0% each), and dizziness (9.7%). • Eighteen patients died during Study 304; only 2 AEs that resulted in death (pneumonia in a 60-year-old White female with a primary diagnosis of MSA and myocardial infarction in a 75-year-old White male with a primary diagnosis of NDAN) were considered to be possibly related to study drug. Two additional deaths occurred outside the study reporting period (one of unknown cause and one of urosepsis); neither were considered to be related to study drug. Additional details on all deaths can be found in Section 7.4.2. • Overall, 83 of 350 (23.7%) patients treated with droxidopa reported a total of 177 SAEs. • Forty-seven (13.4%) patients reported a total of 47 AEs leading to study drug discontinuation. • The incidence of hypertension was low throughout the study and showed no trends over time.

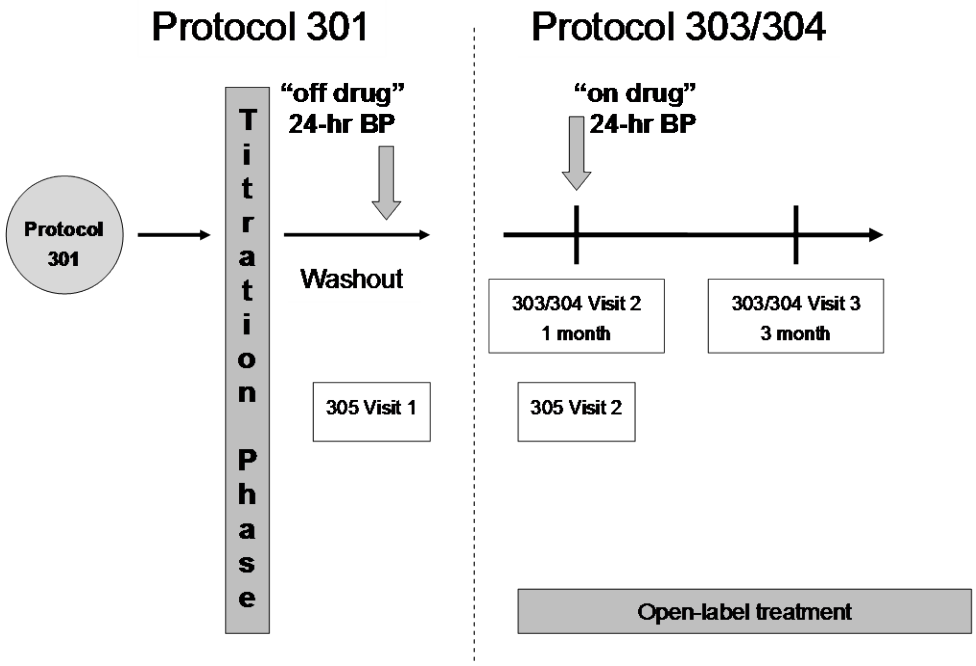
AE=adverse event; BP=blood pressure; DβH=dopamine beta hydroxylase; ECG=electrocardiogram; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event; TID=three times daily.

10.2.6 Study 305

Study 305 was designed to evaluate 24-hour BP changes during treatment with droxidopa. For those patients who participated in Study 305, the 7-day washout period of Study 301 was used to obtain "off-drug" (Baseline) measures. The "on-drug" 24-hour BP measures were obtained after approximately 1 month of treatment with droxidopa in Studies 303 or 304 (Figure 10-2). A total of 20 patients were enrolled in the study. Of these, 18 patients had adequate on-treatment assessments, completed the study according to the protocol, and were included in the safety population.

A tabular summary of the patient population characteristics, study objectives, endpoints, and results is presented in Table 10-7.

Figure 10-2 Study 305: Study Design



BP=Blood pressure

Table 10-7 Description of Study 305

Study Design	Number of Patients/Study Population	Study Objectives	Safety Endpoints	Safety Results
Study 305 was a Phase 3, multi-center, open-label crossover study to assess the effect of droxidopa on 24-hour BP profiles. Blood pressure was measured via ambulatory BP cuff every 30 minutes both off drug, then again when on drug approximately 1 month. Doses of droxidopa ranged from 100 to 600 mg TID.	N=18 Symptomatic nOH in patients with primary autonomic failure, DβH Deficiency, or NDAN (All patients who enrolled in Study 305 were in the post-titration washout phase of Study 301 and had planned to participate in Study 303 or 304.) Mean (SD) Age and Gender (%) at Screening: (n=18) 74 years (6.3) Male: 72% Female: 28%	To determine the effect of droxidopa treatment on the 24-hour BP profiles of patients being treated with droxidopa for approximately 4 weeks.	Vital signs, including: Average 24-hour arterial BP Average nocturnal arterial BP (11 PM to 5 AM) Average diurnal arterial BP (8 AM to 4 PM)	• Droxidopa doses of 100-600 mg TID given over 4 weeks resulted in statistically significant increases in multiple BP measurements. • 24-hour mean SBP increased 7.3 mmHg (p=0.027) and 24-hour mean DBP increased 4.8 mmHg (p=0.003) on drug compared with off drug. • Mean diurnal (8am to 4pm) SBP increased by 8.4 mmHg (p=0.03) on drug compared with off drug. • Mean nocturnal (11pm to 5am) SBP increased by 7.8 mmHg (p=0.13) on drug compared with off drug. • A total of 7 patients had any SBP reading >180 mmHg while on droxidopa; 4 of these 7 had >180 mmHg readings while off drug as well. The majority of these readings were single readings and SBP >180 mmHg did not persist for more than 1 hour. • Results for all other safety variables were reported in Study 301, 303, or 304.

AE=adverse event; BP=blood pressure; DβH=dopamine beta hydroxylase; DBP=diastolic blood pressure; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; SBP=systolic blood pressure; SD=standard deviation; TID=three times daily.

10.2.7 Study 101

Study 101 was a two-part food-effect/BE/PK study. Part I was a randomized, open-label, 3-period crossover study in 24 healthy, elderly, male or female subjects. Subjects were allocated to 1 of 3 treatment sequences according to a randomization schedule prepared prior to the start of the study. Each subject received a single, oral dose of three 100 mg capsules of droxidopa with 240 mL of water either in the fasted state (Treatment A) or immediately following the consumption of a standardized high-fat meal (Treatment B), or a single, oral dose of one 300 mg capsule of droxidopa with 240 mL of water in the fasted state (Treatment C) on Days 1, 4, and 7. Subjects were discharged from the research clinic on Day 8 after completing all post-treatment follow-up assessments and returned to the research clinic approximately 1 week later for Part II of the study. Part II was an open-label design; all subjects received 3 doses of 300 mg droxidopa (three 100 mg capsules/dose) at 4-hour intervals and were followed for a 24-hour period to evaluate the PK profile of droxidopa 300 mg TID.

A tabular summary of the patient population characteristics, study objectives, endpoints, and results is presented in Table 10-8.

Table 10-8 Description of Study 101

Study Design	Number of Patients/Study Population	Study Objectives	Endpoints	Results
Study 101 was a Phase 1, 2-part study: Part I: randomized, OL, 3-period cross-over Part II: OL, 24-hr PK Dose Range: Part I: Three 100-mg capsules vs. single 300-mg capsule Part II: 300 mg TID (every 4 hrs) vs. single 300-mg dose	N=24 Healthy, male and female volunteers ≥65 years of age Mean (SD) Age and Gender (%) at Screening: (n=24) 70.2 years (4.01) Male: 20.8% Female: 79.2%	*Primary:* •evaluate the effects of a high-fat meal on the PK profile of droxidopa and its primary metabolites in healthy, elderly patients •demonstrate the BE of three 100-mg capsules of droxidopa vs. a single 300-mg capsule in healthy, elderly patients •evaluate the PK profile of a 300-mg TID (every 4 hrs) droxidopa dosing regimen in healthy, elderly patients compared to a single dose of 300 mg droxidopa *Secondary:* Confirm the safety of 3 doses or less of droxidopa capsules (no more than 900 mg total daily dose) in healthy, elderly patients	PK/BE: PK parameters for droxidopa were calculated using non-compartmental analysis. Safety: AE monitoring Clinical laboratory parameters Vital signs ECG Physical examination Concomitant medications	• After administration of three 100 mg droxidopa capsules with a high fat / high calorie meal, there was a 2-fold increase in the median T_{max}, a 34% decrease in C_{max}, and a 20% decrease in AUC. These data indicate that there was a reduction in the extent and rate of absorption when droxidopa is administered under fed conditions. • Comparison of the 300 mg single doses in Part I and Part II indicated consistent PK of droxidopa after single doses and 3 doses administered at 4-hour intervals. • There were no TEAEs of clinical significance although without a placebo control, the relatedness of these AEs to droxidopa is not clear. • Droxidopa increased SBP by 10-40 mmHg; increases were transient, corresponding to the time of the peak plasma concentration. In 3 subjects (13%), the increases were judged to be clinically significant. Otherwise, there were no treatment-emergent changes in vital signs.

AE=adverse event; AUC=area under the plasma concentration time curve; BE=bioequivalence; BP=blood pressure; C_{max}=maximum plasma concentration; DβH=dopamine beta hydroxylase; ECG=electrocardiogram; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; PK=pharmacokinetics; SBP=systolic blood pressure; SD=standard deviation; TEAE=treatment-emergent adverse event; TID=three times daily; T_{max}=time of maximum plasma concentration.

10.2.8 Study 102

Study 102 was a randomized, double-blind, single-site, 4-period crossover study in healthy male and female subjects to determine whether droxidopa administered as a single therapeutic (600 mg) and a single supratherapeutic (2000 mg) dose delays cardiac repolarization as determined by the measurement of QTc. Eligible subjects were enrolled and randomly assigned to 1 of 8 treatment sequences. Subjects crossed over into 4 treatment periods where they received a single dose of each of the following treatments under fasting conditions separated by a minimum 3-day washout period (from Day 1 of each period):

- Droxidopa 600 mg (therapeutic dose), oral capsules
- Droxidopa 2000 mg (supratherapeutic dose), oral capsules
- Placebo (matched to droxidopa), oral capsules
- Moxifloxacin 400 mg (positive control; overencapsulated), oral capsules

A total of 52 subjects who were randomly assigned to study drug, and all 52 completed the study and were included in both the safety and PK populations.

A tabular summary of the patient population characteristics, study objectives, endpoints, and results is presented in Table 10-9.

Table 10-9 Description of Study 102

Study Design	Number of Patients/Study Population	Study Objectives	Endpoint	Results
Study 102 was a Phase 1, randomized, double-blind, single-site, 4-period crossover study to determine whether droxidopa administered as a single therapeutic (600 mg) and a single supra-therapeutic (2000 mg) dose delays cardiac repolarization as determined by the measurement of QTc. Dose Range: Droxidopa 600 mg, droxidopa 2000 mg, placebo, and moxi-floxacin 400 mg	N=52 Healthy, male and female volunteers Mean (SD) Age and Gender (%) at Screening: (n=52) 28.9 years (7.26) Male: 51.9% Female: 48.1%	Primary Objective: To define the ECG effects of droxidopa administered orally as a 600 mg therapeutic and a 2000 mg supratherapeutic dose compared with placebo and moxifloxacin in healthy adult male and female subjects. Secondary Objective: To evaluate the safety and PK of droxidopa when administered as a single 600 mg therapeutic and single 2000 mg supratherapeutic dose.	Pharmacodynamics were evaluated by continuous cardiac monitoring. Pharmacodynamic variables included HR, the RR, PR, QRS, and QT intervals, QTcF, QTcB, and QTcI. Safety was evaluated in terms of AEs, clinical laboratory test results (serum chemistry, hematology, and urinalysis), vital sign measurements (BP, HR, respiratory rate, and oral body temperature), safety 12-lead ECG results, and physical examination findings.	• The effect of droxidopa on cardiac repolarization using the QTcI interval showed no signal. • No clear signal of any effect on heart rate, AV conduction, or cardiac depolarization as measured by the PR and QRS interval durations was observed. There were no new clinically relevant morphological changes demonstrating a signal of concern. • The effect of droxidopa on cardiac repolarization using the QTcI interval and the PK/pharmacodynamic relationships showed no signal. • Mean total exposures (AUC_{0-23h}) were 16589 ng*h/mL and 37510 ng*h/mL after a single therapeutic dose (600 mg) and supratherapeutic dose (2000 mg) of droxidopa, respectively. • Mean peak exposures (C_{max}) were 3966 ng/mL and 7923 ng/mL in the 600 mg and 2000 mg droxidopa treatments, respectively. • An increase of 3.3-fold in dose resulted in only 2.3-fold and 2-fold increases in mean total exposure (AUC_{0-inf} and AUC_{0-23h}) and mean C_{max}, respectively. • Maximum concentration of droxidopa peaked at a median T_{max} of approximately 2 hours after administration of 600 mg and 2000 mg treatments of droxidopa. • Mean $t_{1/2}$ was approximately 3 hours for both dose levels. • Overall, the most common AEs were abdominal pain and dermatitis contact (36.5% each), nausea (28.8%), and headache (25.0%). • No deaths, SAEs, or TEAEs leading to study drug discontinuation were reported. • There was a mild increase in mean BP after the 2 droxidopa treatments.

AE=adverse event; AUC=area under the plasma concentration time curve; $AUC_{(0-23h)}$=area under the plasma concentration versus time curve from time 0 to 23 hours; AUC_{0-t}=AUC from time 0 to the last quantifiable concentration data point; AV=atrioventricular; BE=bioequivalence; BP=blood pressure; C_{max}=maximum plasma concentration; DβH=dopamine beta hydroxylase; ECG=electrocardiogram; HR=heart rate; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; PK=pharmacokinetics; QTcB=QT interval corrected with Bazett's formula; QTcI=QT interval corrected using an individual correction method; QTcF=QT interval corrected with Fridericia's formula; SBP=systolic blood pressure; SD=standard deviation; TEAE=treatment-emergent adverse event; TID=three times daily; T_{max}=time of maximum plasma concentration; $t_{1/2}$=apparent terminal half-life.

10.2.9 Study 104

Study 104 was an open-label, randomized, 2-period, 2-treatment, crossover study in healthy male and female fasted subjects. Treatment A (reference treatment: one 100 mg and one 200 mg capsule of droxidopa) and Treatment B (test treatment: a 300 mg capsule of droxidopa) were administered as a single oral dose with 240 mL of water in the fasted state at approximately 8 am on Day 1 and Day 4. Twenty-four subjects were randomized to 1 of 2 sequences (AB or BA). There was a 3-day washout between dosing and 2 days separated the last PK sampling of Period 1 on Day 2 and the first PK sampling of Period 2 on Day 4.

A tabular summary of the patient population characteristics, study objectives, endpoints, and results is presented in Table 10-10.

Table 10-10 Description of Study 104

Study Design	Number of Patients/Study Population	Study Objectives	Endpoint	Results
Study 104 was a Phase 1 Randomized, OL, BE study comparing one 100 mg and one 200 mg capsule of droxidopa with one 300 mg capsule of droxidopa. Dose Range: One 100 mg and one 200 mg capsule vs. single 300 mg capsule	N=24 Healthy, male and female volunteers Mean (SD) Age and Gender (%) at Screening: (n=24): 43 years (13.2) Male: 66.7% Female: 33.3%	Primary Objective: To demonstrate the BE of one 100 mg and one 200 mg capsule of droxidopa versus one 300 mg capsule of droxidopa in healthy subjects. Secondary Objective: To confirm the safety of one 100 mg and one 200 mg capsule of droxidopa versus one 300 mg capsule of droxidopa in healthy subjects.	<u>PK/BE:</u> PK parameters for droxidopa were calculated using non-compartmental analysis. <u>Safety:</u> AE monitoring Clinical laboratory parameters Vital signs ECG Physical examination	• Comparison of one 100 mg and one 200 mg capsule versus one 300 mg capsule indicated consistent PK parameters (C_{max}, AUC, T_{max}, and $t_{1/2}$). • The geometric mean ratios were well within the 80.00% to 125.00% equivalence window, demonstrating dosage form proportionality between the 2 treatments. The bioequivalence of the administration of one 100 mg and one 200 mg capsule of droxidopa compared with one 300 mg capsule was confirmed under fasted conditions. • There were no TEAEs of clinical significance although without a placebo control, the relatedness of these AEs to droxidopa is not clear.

AE=adverse event; AUC=area under the plasma concentration time curve; BE=bioequivalence; BP=blood pressure; C_{max}=maximum plasma concentration; ECG=electrocardiogram; PK=pharmacokinetics; SD=standard deviation; TEAE=treatment-emergent adverse event; T_{max}=time of maximum plasma concentration; $t_{1/2}$=apparent terminal half-life.

10.3 Appendix 3: Independent Report of Site Effects in Study 301

The following is an independent analysis (conducted by Brent Blumenstein, Ph.D.) evaluating Study 301 regarding the heterogeneity of data across the clinical sites with respect to the efficacy outcomes. The features of the analyses are as follows:

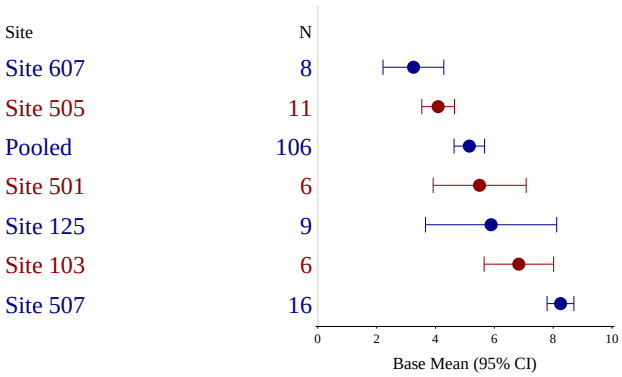
- The variability of outcome across sites is assessed for sites large enough to provide reasonable efficacy estimates.
- There are numerous small sites. These small sites are pooled into a single pseudo-site. The criterion for pooling sites is 2 or fewer patients in either treatment arm. The pseudo-site consists of 106 patients across 44 sites. The pseudo-site is larger than any of the remaining sites. The expectation from the pseudo-site is an estimate of efficacy near the average and, other than assessing whether the estimate from the pseudo-site is more or less as expected, it is ignored.
- Evidence of site heterogeneity is strongly supported when the heterogeneity is consistent across multiple outcomes.
- Site baseline heterogeneity is also relevant to efficacy outcome heterogeneity.

The site between-arm efficacy effects are based on an analysis of variance model with an indicator variable for each site, a variable for arm (0 = control or 1 = experimental), and the interaction between the arm variable and the site variables. The interaction provides an opportunity to assess heterogeneity of between-arm effect across sites. The criterion for evidence of heterogeneity of effect is somewhat arbitrarily set as an interaction P of ≤ 0.10. Please note that the interaction P is a test as to whether any pair of sites differs with respect to the between-arm effect and, therefore, if the interaction P is ≤ 0.10 then, at a minimum, it may be concluded that the largest effect and the smallest effect differ. When the interaction P value meets the 0.10 criterion, the site-specific between-arm effects may range from favoring the control arm to favoring the experimental arm and, therefore, care must be taken to interpret the implications of the range of and relationships between site-specific between-arm effects. Also, note that the interaction P may meet the 0.10 criterion at the same time the overall effect assessed without site in the model may indicate a strong between-arm effect. The existence of a site interaction P meeting the 0.10 criterion does not automatically invalidate an overall primary result, but may have clinical implications.

The primary analysis was to be based on non-parametric assessment of outcome because of lack of normality and, therefore, the failure to find P values meeting the criterion specified for these primary analysis is not material. While the analysis of variance model used here is not ideal given the lack of normality, it does provide a means of crudely assessing for evidence of site effect heterogeneity.

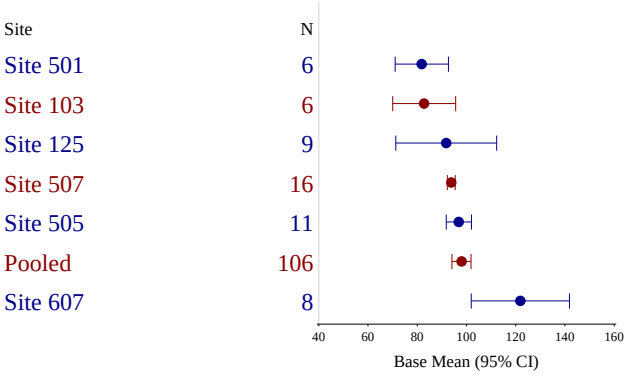
The following figure shows Baseline estimates and 95% confidence intervals for the dizziness/lightheadedness (OHSA Item 1 score) and standing BP measures. This figure illustrates the degree of variability across sites prior to intervention in this double-blind trial and should serve as a benchmark of assessing the variability in outcome. This figure also shows that the largest site has 16 patients (Site 507) and, therefore, has 9.9% (16/162) of the total patients. The next largest site has 11 patients (6.8%). Thus, no one single site dominates accrual.

Dizziness/Lightheadedness



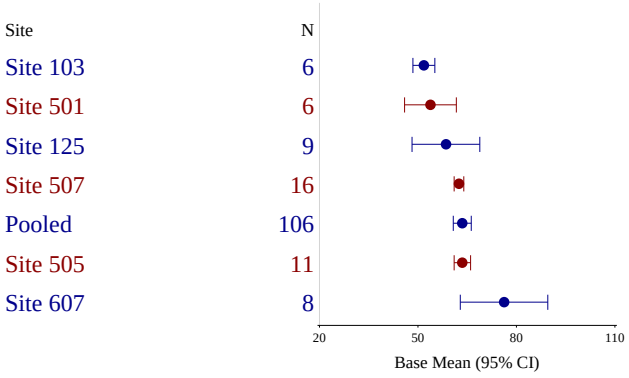
Sites Pooled: <3 in Either Arm

Standing Systolic Blood Pressure



Sites Pooled: <3 in Either Arm

Standing Diastolic Blood Pressure



Sites Pooled: <3 in Either Arm

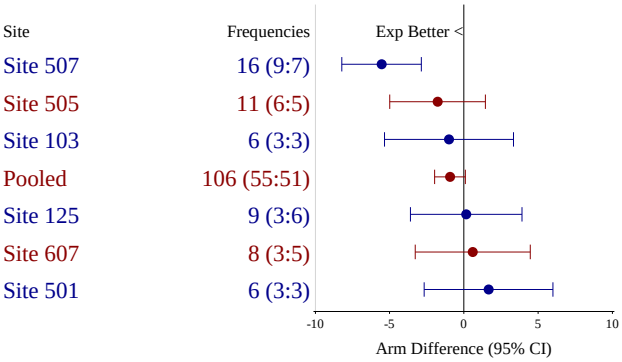
The above figure for dizziness/lightheadedness suggests a wide range of Baseline values. Since dizziness/lightheadedness is a patient-reported outcome, it could be that the Baseline is influenced by the instructions given to the patient at that site. It must also be kept in mind that the dizziness/lightheadedness measure is limited to the range of 0 to 10, and that the higher the Baseline the more "room" there is for a decrease. Therefore, an alternative analysis of dizziness/lightheadedness is to use the percent change.

Also, as can be seen in the above figures, Site 607 has higher Baseline BP values whereas the other sites are relatively homogeneous. There is no explanation for this finding.

The primary efficacy outcome for the dizziness/lightheadedness question and the standing BP measure is the difference between that measured at randomization and at 1 week of following initiation of treatment. The following figure illustrates the variability across sites of these between-arm efficacy outcomes. According to the criterion specified (interaction $P \leq 0.10$), there is evidence of clinical site heterogeneity for dizziness and systolic BP changes, $P = 0.0387$ and $P = 0.0287$, respectively. P values computed under the same distributional assumptions but without site for these outcomes are simple T tests, and the P values are 0.0054 and 0.0226, respectively (and can be contrasted to the pre-specified CMH rank ANCOVA tests of 0.0001 and 0.0006, respectively). Thus, the pre-specified criterion for these endpoints (without sites) has been met and there is also evidence of site heterogeneity of these outcomes across sites. The

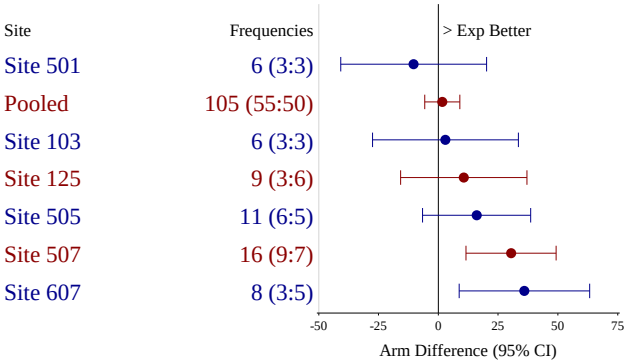
point estimates as shown in the graphs generally suggest an experimental arm effect, consistent with the pre-specified analyses. Also, the results presented in these graphs do not provide a strong suggestion that a single site explains the between-arm efficacy seen in the pre-specified analyses.

Dizziness/Lightheadedness



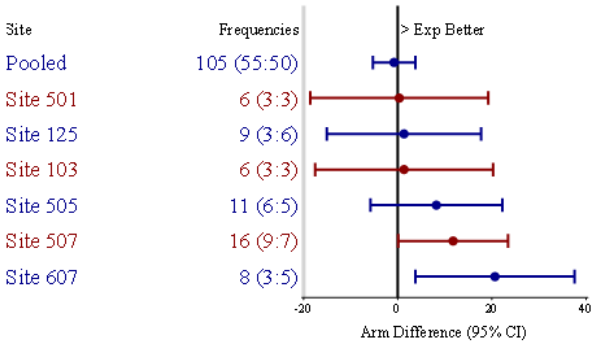
Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.0387

Standing Systolic Blood Pressure



Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.0287

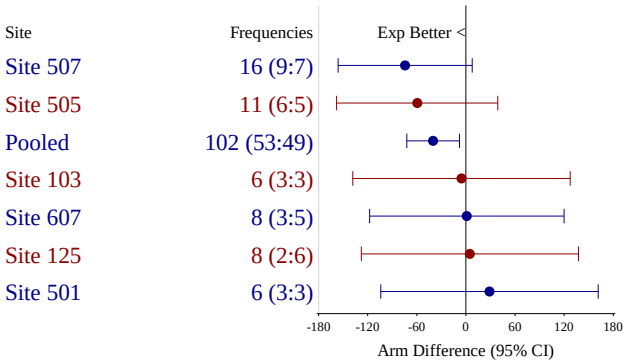
Standing Diastolic Blood Pressure



Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.1448

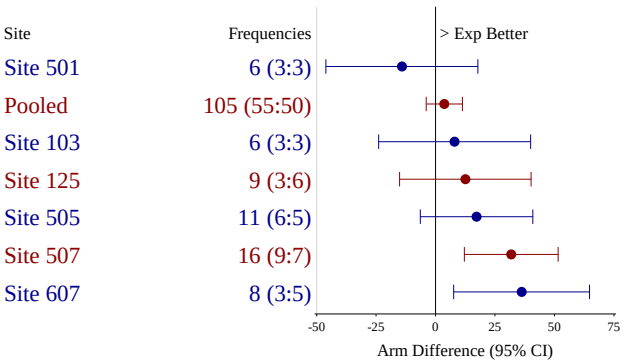
There is, however, a single site in the dizziness/lightheadedness analysis (Site 507) that appears to have a stronger outcome than other sites. It should be noted that Site 507 had the highest Baseline dizziness values. Thus, in an effort to assess the meaning of the higher Baseline values, the next figures are analogous to the previous figures but show the analysis of the percent change as contrasted to the simple change. The interaction P value for dizziness is 0.8051 for the percent change as compared to 0.0387 for the simple change, suggesting that the site heterogeneity for between-arm effect for simple change is an artifact of not accounting for the Baseline. There was no appreciable difference between these analyses (change versus percent change) for either systolic or diastolic BP.

Percent Change in Dizziness



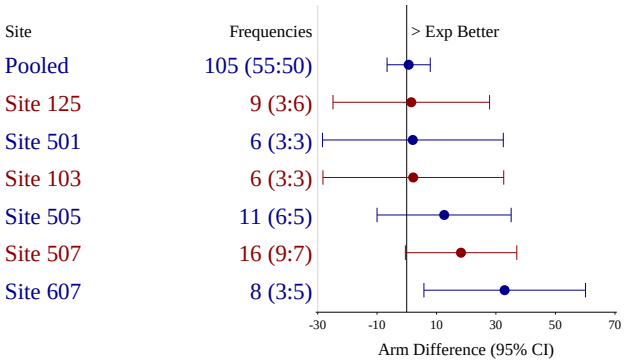
Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.8051

Percent Change in Standing SBP



Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.0450

Percent Change in Standing DBP



Sites Pooled: <3 in Either Arm
Site by Arm Interaction P = 0.2425

10.4 Appendix 4: Summary of Death Adjudications in the Droxidopa Program

Patient Identification	Age and Gender		Type of nOH	Reporter Term(s) as Cause of Death	Droxidopa Dose (TID)	Medically Adjudicated Cause of Death*	Comments
Study 302							
114002	58	M	MSA	Unknown	N/A – in screening	Not evaluated (Screening Patient Only)	
114003	63	F	MSA	Cardiopulmonary Arrest	N/A – Post-study – off drug 11 days	Cardiovascular Death	Sudden, etiology unknown
Study 303							
129002	63	F	MSA	Sudden cardiac death	200 mg	Cardiovascular Death	Sudden, etiology unknown
130002	60	M	MSA	Hypoxic encephalopathy	400 mg	Non-Cardiovascular Death	Respiratory failure /seizure disorder
136001	57	M	PD	Pneumonia	100 mg	Non-Cardiovascular Death	Aspiration pneumonia
136002	81	F	PD	Acute respiratory failure	400 mg	Non-Cardiovascular Death	Sepsis and ARDS
141001	88	M	PD	Pelvic fracture	600 mg	Non-Cardiovascular Death	Insufficient information to determine cause of death
Study 304							
103005	61	M	MSA	Respiratory failure and urosepsis	600 mg	Non-Cardiovascular Death	Pneumonia and respiratory failure
103007	57	M	MSA	Multiple system atrophy	600 mg	Non-Cardiovascular Death	Progressive MSA (history of late stroke but not true cause of death)
105007	56	F	MSA	Pneumonia Sepsis Circulatory collapse	500 mg	Non-Cardiovascular Death	Sepsis and pneumonia
116006	70	F	MSA	Acute respiratory failure	600 mg	Non-Cardiovascular Death	Respiratory failure
125002	78	M	PD	Unknown Cause	600 mg	Indeterminate cause of death	Death occurred 21 days post-study
125006	79	M	MSA	Pneumonia aspiration Sepsis	800 mg/day	Non-Cardiovascular Death	Sepsis
125010	80	M	PD	Cardio-respiratory arrest	600 mg	Cardiovascular Death	Sudden, etiology unknown
501003	55	F	MSA	Brain edema	500 mg	Non-Cardiovascular Death	Suicide (drug overdose)

Patient Identification	Age and Gender		Type of nOH	Reporter Term(s) as Cause of Death	Droxidopa Dose (TID)	Medically Adjudicated Cause of Death*	Comments
145001Z	78	Male	PD	Cardio-respiratory arrest	Stopped study drug 16 days prior to event	Non-Cardiovascular Death	Aspiration pneumonia and respiratory failure that occurred post-operatively while on mechanical ventilation
503004	60	F	MSA	Acute respiratory distress syndrome, pneumonia Pulmonary artery thrombosis	300 mg	Non-Cardiovascular Death	Multi-lobar pneumonia, sepsis
115004A	75	Male	NDAN	Myocardial infarction	400 mg	Non-Cardiovascular Death	Sudden, etiology unknown
113003A	62	Male	PAF	Myocardial infarction	600 mg	Cardiovascular death	Sudden, etiology unknown
113006A	53	Male	MSA	Multiple System Atrophy	600 mg	Non-Cardiovascular Death	Progression of MSA
116002	61	Female	PD	Respiratory Failure	600 mg	Non-Cardiovascular Death	Progression of MSA and respiratory failure
116009	73	Male	MSA	Subdural Hemorrhage	600 mg	Cardiovascular Death	Death due to hemorrhagic stroke (subdural hematoma)
126009	79	Male	PD	Pneumonia	600 mg	Non-Cardiovascular Death	Death due to aspiration pneumonia and respiratory failure
132023Z	83	Female	PD	Respiratory Failure	400 mg	Cardiovascular Death	Sudden death, etiology unknown (possible pulmonary embolism)
146001A	85	Male	PD	Respiratory Failure	600 mg	Non-Cardiovascular Death	Death due to pneumonia
146004A	83	Female	PD	Cardiac Arrest	600 mg	Non-Cardiovascular Death	Death due to hip fracture and post-operative complications
168004A	62	Male	PD	Urosepsis	600 mg	Non-Cardiovascular Death	Death due to sepsis (urinary tract origin)

AE=adverse event; ARDS=Acute Respiratory Distress Syndrome; BP=blood pressure; Disc=discontinued; F=female; incr=increased; inter=interrupted; M=male; MSA=Multiple System Atrophy; N/A=not applicable; NDAN=Non-Diabetic Autonomic Neuropathy; nOH=Neurogenic Orthostatic Hypotension; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; SAE=serious adverse event; TID=three times daily.

10.5 Appendix 5: Listing of SAEs (Fatal and Non-fatal) Reported by Study

This appendix includes all SAEs (fatal and non-fatal) captured in the databases of Studies 301, 302, 303, 304, and 306. In addition, any deaths not captured in the database (occurred outside the pre-specified 7-day reporting window) that the Sponsor is aware of are included for completeness.

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
Study 301										
171009	80	F	PD	Nausea Vomiting	600 mg 600 mg	8/ 1 8/ 1	Moderate Moderate	Probably Probably	Disc Disc	Resolved Resolved
506001	49	M	MSA	Urinary tract infection Ureteric obstruction Neurogenic bladder	300 mg 300 mg 300 mg	11/ 13 11/ 13 11/ 13	Moderate Moderate Moderate	Unlikely Unlikely Unlikely	None None None	Resolved Resolved Resolved
Study 302										
130003	77	M	PD	Coronary artery disease	100 mg	8/ ND	Moderate	Not related	Disc	Ongoing
114002 [4]	58	M	MSA	Unknown	N/A – Prior to Treatment	N/A	Unknown	N/A	N/A	Death
114003 [4]	63	F	MSA	Cardiopulmonary Arrest	N/A - Discontinued	13/2	ND	Not related	N/A	Death
200005	86	M	PAF	Cardiac failure congestive Pneumonia	100 mg 100 mg	6/ 29 6/ 29	Moderate Severe	Not related Not related	None Disc	Resolved Resolved
503001	73	F	PD	Orthostatic hypotension	N/A	16/ 32	Moderate	Not related	None	Resolved
106001	84	F	PD	Mental status changes Urinary tract infection	Placebo Placebo	13/ 3 13/ 17	Moderate Moderate	Unlikely Unlikely	None None	Resolved Resolved
309002	58	F	MSA	Leukopenia	500 mg	19/ 6	Severe	Not related	None	Resolved
Study 303										
100005	81	M	PD	Syncope	300 mg	257/ 2	Moderate	Unlikely	None	Resolved
100006	75	F	PAF	Urinary tract infection	300 mg	493/ 5	Moderate	Unlikely	Inter	Resolved
100007	70	F	MSA	Anxiety Depression	600 mg 600 mg	82/ 10 82/ 10	Severe Severe	Unlikely Unlikely	Disc None	Resolved Resolved
102004	58	F	MSA	Syncope	600 mg	77/ 1	Moderate	Unlikely	None	Resolved
106001	85	F	PD	Atrial fibrillation	200 mg	200/ 68	Moderate	Possibly	None	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
109001	74	F	NDAN	Headache	600 mg	7/ 11	Severe	Definitely	Inter	Resolved
				Loss of consciousness	600 mg	15/ 4	Severe	Definitely	Disc	Resolved
111005	65	M	NDAN	Urinary tract infection	600 mg	301/ 4	Moderate	Not related	None	Resolved
				Respiratory distress	600 mg	370/ 16	Moderate	Unlikely	None	Resolved
113003	60	M	PAF	Angina pectoris	500 mg	91/ 2	Moderate	Unlikely	Inter	Resolved
				Orthostatic hypotension	500 mg	253/ 3	Severe	Unlikely	None	Resolved
115004	73	M	NDAN	Deep vein thrombosis	400 mg	299/ 5	Moderate	Unlikely	Inter	Resolved
				Dehydration	400 mg	501/ 4	Moderate	Unlikely	Inter	Resolved
129002	63	F	MSA	Sudden cardiac death	200 mg	286/ 1	Severe	Not related	None	Death
130002	60	M	MSA	Hypoxic encephalopathy	400 mg	71/ 16	Severe	Possibly	Disc	Death
134001	86	F	MSA	Syncope	200 mg	117/ 2	Severe	Not related	Incr	Resolved
134004	73	M	PD	Bronchial hemorrhage	100 mg	201/ 25	Moderate	Not related	None	Resolved
134005	83	F	PD	Arthralgia	200 mg	174/ 3	Moderate	Not related	None	Resolved
				Coronary artery disease	200 mg	212/ 2	Severe	Not related	None	Resolved
				Hip fracture	200 mg	255/ 6	Severe	Not related	None	Resolved
				Osteoarthritis	200 mg	255/ 6	Severe	Not related	None	Resolved
				Pneumonia	200 mg	373/ 8	Severe	Not related	Inter	Resolved
136001	57	M	PD	Dementia	500 mg	197/ 7	Moderate	Not related	Inter	Resolved
				Post-traumatic stress disorder	500 mg	197/ 7	Moderate	Not related	Inter	Resolved
				Major depression	500 mg	197/ 7	Moderate	Not related	Inter	Resolved
				Pneumonia	100 mg	539/ 33	Moderate	Not related	Disc	Death
136002	81	F	PD	Hip fracture	400 mg	26/ 2	Severe	Unlikely	None	Resolved
				Vertigo	400 mg	223/ 4	Severe	Unlikely	None	Resolved
				Acute respiratory failure	400 mg	414/ 24	Severe	Not related	Disc	Death
141001	88	M	PD	Pelvic fracture	600 mg	247/ 8	Severe	Unlikely	Disc	Death
145001	75	M	PAF	Angina pectoris	100 mg	290/ 4	Severe	Not related	Inter	Resolved
146009	72	M	PD	Hip fracture	500 mg	222/ 1	Severe	Unlikely	Inter	Resolved
161001	74	M	PAF	Malignant tumor excision	400 mg	37/ 1	Mild	Not related	None	Resolved
				Malignant tumor excision	400 mg	37/ 1	Mild	Not related	None	Resolved
168003	86	M	PD	Diverticulum	200 mg	59/ 3	Moderate	Not related	None	Resolved
				Cervical vertebral fracture	100 mg	159/ 46	Severe	Unlikely	None	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
401016	55	M	MSA	Contusion	600 mg	92/ 11	Moderate	Not related	None	Resolved
				Syncope	600 mg	92/ 1	Moderate	Not related	None	Resolved
				Fall	600 mg	92/ 1	Moderate	Not related	None	Resolved
				Facial bones fracture	600 mg	92/ 11	Moderate	Not related	None	Resolved
402005	66	F	MSA	Renal failure acute	200 mg	38/ 19	Severe	Not related	Disc	Other[3]
403002	62	M	MSA	Venous thrombosis limb	600 mg	27/ ND	Moderate	Unlikely	None	Ongoing
406001	68	F	PD	Agitation	100 mg	85/ ND	Moderate	Possibly	Disc	Ongoing
				Hallucination, visual	100 mg	85/ ND	Moderate	Possibly	Disc	Ongoing
504006	66	M	PD	Confusional state	600 mg	13/ 52	Moderate	Possibly	None	Resolved
				Hallucination	600 mg	13/ 52	Moderate	Possibly	Disc	Resolved
Study 304 [5]										
100001	24	F	PAF	Pregnancy	600 mg	422/119	Severe	Not related	Disc	Resolved
100005A	83	M	PD	Head injury	300 mg	196/4	Moderate	Not related	None	Resolved
				Hallucination	300 mg	197/3	Moderate	Not related	None	Resolved
100006	76	M	PAF	Traumatic intracranial hemorrhage	600 mg	167/7	Moderate	Not related	None	Resolved
				Inguinal hernia	600 mg	407/2	Moderate	Not related	None	Resolved
				Aortic aneurysm	600 mg	513/2	Moderate	Not related	None	Resolved
				Fall	600 mg	817/4	Moderate	Not related	None	Resolved
				Inguinal hernia	600 mg	894/2	Moderate	Not related	None	Resolved
				Chest discomfort	600 mg	913/ 5	Moderate	Unlikely	None	Resolved
				Dyspnea	600 mg	913/ 5	Moderate	Unlikely	None	Resolved
100007	77	M	PAF	Hypertensive crisis	600 mg	104/17	Moderate	Unlikely	Disc	Resolved
103005	61	M	MSA	Respiratory failure	600 mg	598/3	Severe	Not related	None	Death
103007	57	M	MSA	Cerebral infarction	600 mg	146/ND	Severe	Unlikely	None	Ongoing
				Carotid artery thrombosis	600 mg	146/1	Severe	Unlikely	None	Death
105002	67	M	MSA	Hypotension	600 mg	652/39	Moderate	Not related	None	Resolved
				Skin laceration	600 mg	827/1	Moderate	Possibly	Decr	Resolved
				Urinary tract infection	600 mg	862/ND	Mild	Not related	None	Ongoing

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
105006	66	F	PD	Pneumonia aspiration	400 mg	325/7	Moderate	Not related	Inter	Resolved
				Aspiration	500 mg	658/51	Moderate	Not related	Inter	Resolved
105007	56	F	MSA	Pneumonia	500 mg	118/ND	Moderate	Not related	None	Ongoing
				Sepsis	500 mg	126/ND	Moderate	Not related	None	Ongoing
				Circulatory collapse	500 mg	128/1	Moderate	Not related	Disc	Death
106001Z	67	F	PD	Skin laceration	300 mg	295/62	Moderate	Unlikely	None	Resolved
112002Z	68	F	PD	Cerebrovascular accident	400 mg	120/3	Mild	Possibly	Disc	Resolved
113002Z	73	F	PD	Hemorrhage	300 mg	278/4	Moderate	Unlikely	None	Resolved
113003A	62	M	PAF	Myocardial infarction	600 mg	550/1	Severe	Not related	Disc	Death
113003Z	72	M	PD	Lower gastrointestinal hemorrhage	600 mg	151/9	Moderate	Unlikely	Inter	Resolved
				Colitis ischemic	600 mg	151/9	Moderate	Unlikely	Inter	Resolved
				Deep vein thrombosis	600 mg	163/2	Moderate	Unlikely	None	Resolved
				Deep vein thrombosis	600 mg	163/2	Moderate	Unlikely	None	Resolved
113004	67	M	PD	Fall	300 mg	1021/3	Severe	Not related	None	Resolved
113005A	73	M	MSA	Benign prostatic hyperplasia	600 mg	169/2	Mild	Not related	Inter	Resolved
113006A	53	M	MSA	Multiple system atrophy	600 mg	777/1	Severe	Not related	None	Death
114002Z	60	M	PD	Heat stroke	400 mg	166/3	Severe	Unlikely	Inter	Resolved
				Localized infection	400 mg	252/10	Moderate	Not related	Inter	Resolved
115003Z	69	M	PD	Non-cardiac chest pain	600 mg	397/5	Moderate	Not related	Inter	Resolved
				Dyspnea	600 mg	397/5	Moderate	Not related	Inter	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
115004A	75	M	NDAN	Back pain	400 mg	139/6	Moderate	Not related	None	Resolved
				Constipation	400 mg	139/6	Moderate	Not related	None	Resolved
				Urinary retention	400 mg	139/6	Moderate	Not related	None	Resolved
				Pneumonia	400 mg	225/7	Moderate	Not related	Inter	Resolved
				Pancytopenia	400 mg	233/11	Moderate	Not related	Inter	Chronic stable condition
				Pleural effusion	400 mg	330/9	Moderate	Not related	None	Resolved
				Pneumonia	400 mg	330/9	Moderate	Not related	None	Resolved
				Myocardial infarction	400 mg	363/1	Severe	Possibly	Disc	Death
115005Z	79	M	PD	Gait disturbance	300 mg	266/ND	Mild	Unlikely	None	Resolved
				Pain in extremity	300 mg	266/ND	Mild	Unlikely	None	Resolved
116002	61	F	PD	Respiratory failure	600 mg	1033/1	Severe	Not related	Disc	Death
116006	70	F	MSA	Multiple System Atrophy	600 mg	268 [6]/ND	Severe	Not related	Inter	Ongoing
				Acute respiratory failure	600 mg	443/5	Severe	Not related	Disc	Death
				Aspiration	600 mg	443/ND	Severe	Not related	Inter	Ongoing
				Dysphagia	600 mg	443/ND	Severe	Not related	Inter	Ongoing
116009	73	M	MSA	Subdural hemorrhage	600 mg	ND [6]/ND	Severe	Not related	Disc	Death
				Dehydration	600 mg	718/5	Moderate	Unlikely	None	Resolved
				Pain in extremity	600 mg	718/5	Mild	Not related	None	Resolved
				Urinary tract infection	600 mg	718/5	Mild	Unlikely	None	Resolved
117001	75	M	PD	Orthostatic hypotension	500 mg	81/3	Moderate	Not related	Disc	Resolved
117007	75	M	PD	Atrial flutter	500 mg	116/1	Moderate	Possibly	None	Resolved
117010	84	F	Other	Cholecystitis	600 mg	211/4	Moderate	Not related	None	Resolved
118003Z	69	M	PD	Fall	300 mg	532/3	Moderate	Unlikely	None	Resolved
118005Z	80	M	PD	Chest pain	100 mg	74/2	Severe	Unlikely	Inter	Resolved
				Hypertension	100 mg	272/96	Mild	Possibly	None	Resolved
				Non-cardiac chest pain	100 mg	272/3	Moderate	Unlikely	None	Resolved
				Hyponatremia	100 mg	273/2	Moderate	Unlikely	None	Resolved
122002Z	75	M	PD	Transient ischemic attack	600 mg	346/1	Mild	Not related	None	Resolved
122003Z	68	F	PD	Suicide attempt	600 mg	114/1	Severe	Not related	Disc	Resolved
				Depression	600 mg	114/15	Severe	Not related	None	Resolved
122009Z	71	F	PD	Dehydration	300 mg	84/ND	Severe	Not related	None	Ongoing
				Syncope	300 mg	84/1	Severe	Not related	Disc	Resolved
122011Z	70	M	PD	Pneumonia	600 mg	272/ND	Severe	Not related	None	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
124004	38	F	PAF	Sepsis Intervertebral disc protrusion	400 mg 400 mg	141/8 344/3	Severe Moderate	Not related Not related	None Inter	Resolved Resolved
125002 [4]	78	M	PD	Unknown cause	600 mg	439 / ND	ND	ND	ND	Death
125006	79	M	MSA	Pneumonia aspiration Sepsis	800 mg/day [7] 800 mg/day [7]	453/ND 453/20	Severe Severe	Not Related Not related	None Disc	Ongoing Death
125010	80	M	PD	Cardio-respiratory arrest	600 mg	37/2	Severe	Unlikely	Disc	Death
125017	65	M	PD	Mental status changes	600 mg	413/ND	Severe	Not related	Disc	Ongoing
126003	80	M	PD	Transient ischemic attack	400 mg	59/2	Moderate	Unlikely	Disc	Resolved
126004	76	F	PD	Syncope	600 mg	296/3	Mild	Not related	None	Resolved
126005	71	F	PD	Bladder cancer	500 mg	353/72	Moderate	Not related	None	Resolved
126009	79	M	PD	Pneumonia Pneumonia Supraventricular tachycardia Pneumonia aspiration	600 mg 600 mg 600 mg 600 mg	148/13 419/5 579/6 735/2	Mild Moderate Moderate Severe	Not related Not related Not related Not related	Inter Inter Inter Disc	Resolved Resolved Resolved Death
126010	70	M	PD	Syncope	600 mg	150/2	Moderate	Unlikely	Inter	Resolved
127002	75	M	PD	Orchitis	500 mg	560/5	Mild	Unlikely	None	Resolved
131007Z	75	M	PD	Orthostatic hypotension	500 mg	66/ND	Severe	Unlikely	None	Resolved
132017Z	78	M	PD	Cardiac failure congestive	300 mg	244/3	Mild	Unlikely	Disc	Resolved
132023Z	83	F	PD	Humerus fracture Femur fracture Respiratory failure	(400 mg at last visit, 55 days prior to the 2 fractures and 100 days prior to respiratory failure)	144/1 144/1 189/1	Moderate Moderate Severe	Not related Not related Not related	None None Disc	Resolved Resolved Death
134001A	88	F	MSA	Spinal fracture BP fluctuation Pneumonia	400 mg 400 mg 400 mg	66/12 321/ND 447/ND	Moderate Severe Severe	Unlikely Unlikely Unlikely	None None None	Resolved Ongoing Resolved
135002Z	74	M	PD	Hip fracture	600 mg	611/1	Severe	Not related	None	Resolved
137002Z	71	M	PD	Hypertension	100 mg	6/2	Severe	Definitely	Disc	Resolved
140001A	81	M	PD	Parkinson's disease Herpes zoster oticus	500 mg 500 mg	379/3 379/3	Moderate Moderate	Not related Not related	None None	Resolved Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
145001Z	78	M	PD	Urinary tract infection	600 mg	28/69	Severe	Unlikely	None	Resolved
				Diverticulitis	600 mg	45/53	Severe	Unlikely	None	Resolved
				Peridiverticular abscess	600 mg	45/53	Severe	Unlikely	None	Resolved
				Dehydration	600 mg	49/3	Severe	Unlikely	None	Resolved
				Hypovolemia	600 mg	49/3	Severe	Unlikely	None	Resolved
				Diarrhea	600 mg	49/3	Severe	Unlikely	None	Resolved
				Cardio-respiratory arrest	200 mg	104/1	Severe	Unlikely	Disc	Death
146001A	85	M	PD	Parkinson's disease	600 mg	549/ND	Severe	Not related	None	Ongoing
				Pneumonia		549/ND	Severe	Not related	Disc	Ongoing
				Respiratory arrest		549/9	Severe	Not related	None	Death
146003A	82	F	PD	Acute respiratory failure	600 mg	124/15	Moderate	Not related	Inter	Resolved
				Bradycardia	600 mg	124/15	Moderate	Not related	Inter	Resolved
				Aspiration	600 mg	243/5	Severe	Not related	Inter	Resolved
				Respiratory failure	600 mg	243/5	Severe	Not related	Disc	Resolved
146004A	83	F	PD	Hip fracture	600 mg	335/2	Severe	Not related	None	Resolved
				Hip fracture	600 mg	353/1	Severe	Not related	None	Resolved
				Syncope	600 mg	353/1	Severe	Not related	None	Resolved
				Cardiac arrest	600 mg	530/1	Severe	Not related	Disc	Death
				Hip fracture	600 mg	530/ND	Severe	Not related	Inter	Ongoing
152003Z	63	M	PD	Psychotic disorder	200 mg	48/6	Severe	Possibly	None	Resolved
				Hallucination	200 mg	48/6	Severe	Possibly	Disc	Resolved
153003Z	76	M	PD	Mental status changes	200 mg	39/5	Severe	Unlikely	None	Resolved
				Asthenia	200 mg	39/5	Severe	Unlikely	None	Resolved
153005Z	82	M	PD	Hip fracture	500 mg	42/3	Severe	Not related	Inter	Resolved
154001Z	81	F	PD	Dehydration	400 mg	351/7	Severe	Not related	None	Resolved
				Diarrhea	400 mg	351/7	Severe	Not related	None	Resolved
161003	65	M	MSA	Pleural effusion	400 mg	786/5	Moderate	Not related	None	Resolved
161004Z	82	M	PD	Syncope	200 mg	26/1	Severe	Unlikely	Inter	Resolved
162002Z	71	F	PD	Upper limb fracture	400 mg	61/4	Severe	Not related	None	Resolved
				Fracture malunion	400 mg	64/91	Severe	Not related	None	Resolved
				Osteoarthritis	600 mg	322/4	Severe	Not related	None	Resolved
162004Z	71	M	PD	Constipation	400 mg	23/3	Severe	Unlikely	None	Resolved
				Fall	400 mg	40/5	Severe	Not related	None	Resolved
				Orthostatic hypotension	400 mg	40/5	Severe	Not related	None	Resolved
				Syncope	400 mg	40/5	Severe	Not related	None	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
163003Z	74	F	PD	Atrial fibrillation	200 mg	87/4	Moderate	Unlikely	None	Resolved
				Syncope	200 mg	87/4	Moderate	Unlikely	None	Resolved
				Syncope	200 mg	194/6	Moderate	Not related	Inter	Resolved
163004Z	79	F	PD	Cerebral infarction	600 mg	580/3	Moderate	Unlikely	Disc	Resolved
165002	70	M	PD	Decubitus ulcer	300 mg	98/53	Severe	Not related	None	Resolved
				Asthenia	300 mg	115/77	Severe	Unlikely	None	Resolved
168004A[4]	62	M	PD	Dehydration	600 mg	477/ND	Severe	Not related	Disc	Ongoing
				Urosepsis	600 mg	500/1	ND	Not related	None	Death
168009	78	F	PD	Viral infection	200 mg	695/2	Moderate	Not related	Inter	Resolved
170008	83	M	PD	Urosepsis	500 mg	110/5	Moderate	Not related	None	Resolved
				Pulmonary embolism	500 mg	523/ND	Moderate	Unlikely	None	Ongoing
171008	82	F	PD	Encephalopathy	400 mg	537/4	Severe	Unlikely	Inter	Resolved
				Malignant hypertension	400 mg	537/4	Severe	Unlikely	Disc	Resolved
173003Z	71	M	PD	Asthenia	200 mg	99/2	Severe	Not related	None	Resolved
174001	63	M	MSA	Aggression	600 mg	255/119	Moderate	Possibly	None	Resolved
				Syncope	600 mg	454/3	Moderate	Not related	None	Resolved
176001Z	85	F	PD	Dehydration	600 mg	295/2	Moderate	Unlikely	Inter	Resolved
				Aortic stenosis	600 mg	377/ND	Moderate	Unlikely	Disc	Ongoing
				Lobar pneumonia	600 mg	377/24	Moderate	Unlikely	None	Resolved
178003Z	75	F	PD	Syncope	600 mg	395/3	Moderate	Unlikely	Inter	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
179002	49	F	PD	Hyperparathyroidism primary	200 mg	79/ 5	Moderate	Unlikely	Inter	Resolved
				Parathyroid tumor benign	200 mg	83/1	Moderate	Not related	None	Resolved
				Pyelonephritis	200 mg	95/4	Moderate	Unlikely	None	Resolved
				Altered state of consciousness	200 mg	103/6	Severe	Unlikely	Disc	Resolved with sequelae
181001Z	75	M	PD	Syncope	200 mg	303/1	Moderate	Unlikely	None	Resolved
				Acute psychosis	200 mg	387/29	Severe	Unlikely	None	Resolved
182005Z	74	M	PD	Skin laceration	600 mg	64/4	Severe	Not related	Decr	Resolved
				Presyncope	600 mg	64/4	Severe	Not related	Decr	Resolved
				Hypovolemia	600 mg	64/4	Severe	Not related	Decr	Resolved
183001Z	74	M	PD	Intervertebral disc protrusion	300 mg	442/5	Moderate	Not related	Inter	Resolved
				Lumbar spinal stenosis	300 mg	442/5	Moderate	Not related	Inter	Resolved
300005	73	F	PAF	Transient ischemic attack	600 mg	329/1	Mild	Unlikely	Disc	Resolved
404002	70	M	MSA	Hypertensive crisis	600 mg	105/2	Severe	Probably	Disc	Resolved
501003	55	F	MSA	Atrial fibrillation	500 mg	34/18	Severe	Unlikely	Disc	Resolved
				Brain edema	500 mg	51/5	Severe	Not related	None	Death
503004	60	F	MSA	Acute respiratory distress syndrome	300 mg	169/ND	Severe	Possibly	None	Ongoing
				Pneumonia	300 mg	169/17	Severe	Possibly	Disc	Death
				Hemorrhagic infarction	300 mg	169/ND	Severe	Unlikely	None	Ongoing
				Hyperthermia	300 mg	169/ND	Severe	Possibly	None	Ongoing
				Pulmonary infarction	300 mg	169/ND	Severe	Unlikely	None	Ongoing
				Pneumonia	300 mg	169/ND	Severe	Possibly	None	Ongoing
				Decubitus ulcer	300 mg	169/ND	Severe	Unlikely	None	Ongoing
				Pulmonary artery thrombosis	300 mg	169/ND	Severe	Not related	None	Ongoing
				Deep vein thrombosis	300 mg	169/ND	Severe	Not related	None	Ongoing
514001	59	M	PD	Suicide attempt	500 mg	169/1	Severe	Possibly	Disc	Resolved
601004	76	F	Other	Dehydration	200 mg	38/2	Moderate	Not related	None	Resolved
Study 306										
122013	80	F	PD	Syncope	Placebo	7/3	Severe	Not related	None	Resolved
132027	86	M	PD	Viral infection	Placebo	57/4	Moderate	Not related	None	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of event	Day on Study[1]/ Duration (days)	Severity	Relationship	Drug Action [2]	Outcome
146006	62	M	PD	Fibula fracture	Placebo	33/ND	Moderate	Not related	None	Ongoing
				Syncope		33/1	Moderate	Not related	Disc	Resolved
151007	82	M	PD	Asthenia	Placebo	70/6	Moderate	Unlikely	Inter	Resolved
110006[8]	77	M	PD	Atrial fibrillation	300 mg	12/76	Moderate	Probably	Disc	Resolved
146008	70	M	PD	Faecaloma	100 mg	32/4	Moderate	Not related	Inter	Resolved
146010	59	M	PD	Inguinal hernia	100 mg	5/2	Severe	Not related	Inter	Resolved
156007	76	M	PD	Upper respiratory tract infection bacterial	400 mg	15/25	Severe	Not related	None	Resolved
				Bronchitis viral	400 mg	15/25	Severe	Not related	None	Resolved
				Mental status changes	400 mg	20/1	Moderate	Possibly	Disc	Resolved
				Presyncope	400 mg	20/1	Moderate	Possibly	None	Resolved
184003	79	F	PD	Abdominal pain upper	300 mg	5/4	Severe	Definitely	None	Resolved
				Hypertension	300 mg	5/4	Severe	Definitely	Disc	Resolved

AE=adverse event; BP=blood pressure; Disc=discontinued; F=female; incr=increased; inter=interrupted; M=male; MSA=Multiple System Atrophy; ND=not determined; NDAN=Non-Diabetic Autonomic Neuropathy; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; SAE=serious adverse event; TID=three times daily.

Note: Due to the titration design of the studies, adjustments to doses as allowed in the protocols, and up-titration occurring in the evening after a study visit with assessments at the previous dose, determining a patient's exact dose can be problematic for some patients. These tables represent the best estimate of dose at time of event drawn from by-patient listings of study medication, visit dates, adverse events, and titration visits.

Note: For patients who died, the dose at time of event is the last dose prior to the event.

1 Study day equals day of onset of AE minus first day of treatment +1.

2 Drug action taken: disc=study drug discontinued; incr=study drug dose increased; inter=study drug interrupted; none=no interruption of study drug.

3 In Patient 402005, the event of renal failure acute did not resolve, it worsened to chronic renal failure.

4 Four deaths were not captured in their respective study database: Patient 114002 (death occurred prior to completing Screening; Study 302); Patient 114003 (death occurred after treatment discontinuation and was not entered into study database, information from the CIOMS is included here; Study 302); Patient 125002 (death noted in Study 304 follow-up listing); Patient 168004A experienced a fatal SAE of urosepsis 23 days after discontinuation of study drug due to an SAE of dehydration.

5 Patient ID numbers were unique to individual studies, not to the entire development program, and duplication of patient ID numbers exist. To prevent confusion, patients who entered Study 304 from Study 303 are marked with an "A" at the end of their patient ID and patients from Study 306 were marked with a "Z". Caution should be exercised when aggregating data across studies given the potential for miscounting of subjects.

6 Patient 116009 did not have a recorded start date for the AE leading to death.

7 Patient 125006 took doses of 200 mg, 200 mg, then 400 mg droxidopa daily.

8 Patient 110006 was randomized to the placebo group, but was mistakenly treated with droxidopa for 3 days.

10.6 Appendix 6: Listing of TEAEs Leading to Study Discontinuation by Study

This appendix includes all TEAEs leading to discontinuation captured in the databases of Studies 301, 302, 303, 304, and 306.

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Day on Study [1]/ Duration (days)	Severity	Relationship	SAE	Outcome
Study 301										
106003	64	M	PD	Hypertension	100 mg	2/ 1	Mild	Probably	No	Resolved
107002	58	M	PAF	Dizziness	100 mg	1/ 10	Mild	Possibly	No	Resolved
116011	69	F	MSA	Irritability	100 mg	1/ 1	Moderate	Probably	No	Resolved
121003	72	F	PD	Tremor	100 mg	3/ ND	Moderate	Possibly	No	Ongoing
124001	74	M	PAF	Asthenia	0 mg	10/ 1	Severe	Not related	No	Resolved
124006	71	M	PAF	Palpitations	300 mg	3/ 1	Moderate	Possibly	No	Resolved
126004	76	F	PD	Nausea	500 mg	5/ 5	Mild	Probably	No	Resolved
169001	76	F	PD	Nausea	500 mg	8/ 1	Moderate	Possibly	No	Resolved
171009	80	F	PD	Nausea	600 mg	8/ 1	Moderate	Probably	Yes	Resolved
				Vomiting	600 mg	8/ 1	Moderate	Probably	Yes	Resolved
400004	53	M	MSA	Hypertension	200 mg	3/ 1	Mild	Probably	No	Resolved
502006	54	F	PAF	Diabetes mellitus	0 mg	13/ ND	Mild	Not related	No	Ongoing
511001	40	M	PAF	BP increased	300 mg	4/ 1	Moderate	Possibly	No	Resolved
514002	67	F	PAF	Nausea	100 mg	1/ 1	Mild	Probably	No	Resolved
Study 302										
101006	70	F	PAF	Troponin increased	100 mg	1/ 1	Mild	Not related	No	Resolved
101007	79	F	PAF	Atrial flutter	300 mg	22/ ND	Mild	Unlikely	No	Ongoing
105001	54	M	MSA	Hypertension	100 mg	2/ 1	Moderate	Definitely	No	Resolved
109001	74	F	NDAN	Loss of consciousness	600 mg	19/ 1	Severe	Definitely	No	Resolved
119003	81	F	PD	Dizziness	300 mg	4/ ND	Moderate	Possibly	No	Ongoing
122003	67	M	PD	Angina pectoris	100 mg	1/ 1	Moderate	Not related	No	Resolved
123002	77	M	MSA	Dizziness	100 mg	4/ 2	Moderate	Probably	No	Resolved
123003	69	M	PAF	Dizziness	100 mg	3/ 1	Moderate	Definitely	No	Resolved
125001	82	M	PD	Dehydration	400 mg	5/ 1	Moderate	Unlikely	No	Resolved
130003	77	M	PD	Coronary artery disease	100 mg	8/ ND	Moderate	Not related	Yes	Ongoing
143001	81	M	PD	Ocular hyperemia	100 mg	2/10	Mild	Not related	No	Resolved
143002	60	M	PD	Syncope	200 mg	22/ 1	Moderate	Not related	No	Resolved
200005	86	M	PAF	Pneumonia	100 mg	6/ 29	Severe	Not related	Yes	Resolved
402003	69	F	PD	Palpitations	200 mg	15/ 3	Mild	Possibly	No	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Day on Study [1]/ Duration (days)	Severity	Relationship	SAE	Outcome
405002	50	M	PD	Visual field defect	200 mg	3/ 3	Moderate	Probably	No	Resolved
Study 303										
100007	70	F	MSA	Anxiety	600 mg	82/ 10	Severe	Unlikely	Yes	Resolved
109001	74	F	NDAN	Loss of consciousness	600 mg	15/ 4	Severe	Definitely	Yes	Resolved
113002	40	M	NDAN	Headache	300 mg	31/ ND	Severe	Probably	No	Ongoing
122006	69	M	PD	Amnesia	300 mg	187/ ND	Mild	Unlikely	No	Ongoing
130002	60	M	MSA	Hypoxic encephalopathy	400 mg	71/ 16	Severe	Possibly	Yes	Death
134005	83	F	PD	Hypertension	200 mg	373/ 8	Moderate	Possibly	No	Resolved
136001	57	M	PD	Pneumonia	100 mg	539/ 33	Moderate	Not related	Yes	Death
136002	81	F	PD	Acute respiratory failure	400 mg	414/ 24	Severe	Not related	Yes	Death
141001	88	M	PD	Pelvic fracture	600 mg	247/ 8	Severe	Unlikely	Yes	Death
168001	80	M	PD	Cognitive disorder	400 mg	ND/ ND	Moderate	Unlikely	No	Ongoing
204002	73	M	PD	Ventricular extrasystoles	200mg	28/ ND	Moderate	Probably	No	Ongoing
401013	53	M	PD	Chest pain	200 mg	265/ 11	Moderate	Possibly	No	Resolved
402005	66	F	MSA	Renal failure acute	200 mg	38/ 19	Severe	Not related	Yes	Other [2]
406001	68	F	PD	Agitation Hallucination, visual	100 mg 100 mg	85/ ND 85/ ND	Moderate Moderate	Possibly Possibly	Yes Yes	Ongoing Ongoing
502002	44	F	Other	Rash	600 mg	28/ ND	Moderate	Possibly	No	Ongoing
504006	66	M	PD	Hallucination	600 mg	13/ 52	Moderate	Possibly	Yes	Resolved
Study 304 [3]										
100001	24	F	PAF	Pregnancy	600 mg	422/119	Severe	Not related	Yes	Resolved
100007	77	M	PAF	Hypertensive crisis	600 mg	104/17	Moderate	Unlikely	Yes	Resolved
101010A[4]	64	M	PAF	Neuropathy peripheral	500 mg	ND/107	Mild	Possibly	No	Resolved
103007	57	M	MSA	Multiple system atrophy	600 mg	86/ND	Severe	Not related	No	Ongoing
105007[7]	56	F	MSA	Circulatory collapse	500 mg	128/1	Moderate	Not related	Yes	Death
108002Z	66	F	PD	Hepatic enzyme increased	600 mg	616/ND	Moderate	Not related	No	Ongoing
112002Z	68	F	PD	Cerebrovascular accident	400 mg	120/3	Mild	Possibly	Yes	Resolved
113003A	62	M	PAF	Myocardial infarction	600 mg	550/1	Severe	Not related	Yes	Death
115004A	75	M	NDAN	Myocardial infarction	400 mg	363/1	Severe	Possibly	Yes	Death
116002	61	F	PD	Respiratory failure	600 mg	1033/1	Severe	Not related	Yes	Death
116006	70	F	MSA	Acute respiratory failure	600 mg	443/5	Severe	Not related	Yes	Death
116009	73	M	MSA	Subdural hemorrhage	600 mg	ND/ND	Severe	Not related	Yes	Death
117001	75	M	PD	Orthostatic hypotension	500 mg	81/3	Moderate	Not related	Yes	Resolved
122003Z	68	F	PD	Suicide attempt	600 mg	114/1	Severe	Not related	Yes	Resolved

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Day on Study [1]/ Duration (days)	Severity	Relationship	SAE	Outcome
122004A	80	M	PD	BP increased	500 mg	265/ND	Moderate	Unlikely	No	Ongoing
122009Z	71	F	PD	Syncope	300 mg	84/1	Severe	Not related	Yes	Resolved
125006	79	M	MSA	Sepsis	800 mg/day	453/20	Severe	Not related	Yes	Death
125010	80	M	PD	Cardio-respiratory arrest	600 mg	37/2	Severe	Unlikely	Yes	Death
125017	65	M	PD	Mental status changes	600 mg	413/ND	Severe	Not related	Yes	Ongoing
126003	80	M	PD	Transient ischemic attack	400 mg	59/2	Moderate	Unlikely	Yes	Resolved
126009	79	M	PD	Pneumonia aspiration	600 mg	735/2	Severe	Not related	Yes	Death
127008	83	F	PD	Intraocular pressure increased	500 mg	46/ND	Moderate	Probably	No	Ongoing
132017Z	78	M	PD	Cardiac failure congestive	300 mg	244/3	Mild	Unlikely	Yes	Resolved
132023Z	83	F	PD	Respiratory failure	400 mg	189/1	Severe	Not related	Yes	Death
135002Z	74	M	PD	Fall	600 mg	610/1	Moderate	Not related	No	Resolved
137002Z	71	M	PD	Hypertension	100 mg	6/2	Severe	Definitely	Yes	Resolved
141002Z	79	M	PD	Balance disorder	400 mg	29/ND	Moderate	Unlikely	No	Ongoing
145001Z	78	M	PD	Cardio-respiratory arrest	200 mg	104/1	Severe	Unlikely	Yes	Death
146001A	85	M	PD	Pneumonia	600 mg	549/ND	Severe	Not related	Yes	Ongoing
146003A	82	F	PD	Respiratory failure	600 mg	243/5	Severe	Not related	Yes	Resolved
146004A	83	F	PD	Cardiac arrest	600 mg	530/1	Severe	Not related	Yes	Death
146012Z	77	M	PD	Edema peripheral	200 mg	23/ND	Mild	Probably	No	Ongoing
152003Z	63	M	PD	Hallucination	200 mg	48/6	Severe	Possibly	Yes	Resolved
156005Z	63	F	PD	Orthostatic hypotension	500 mg	87/39	Moderate	Not related	No	Other: (Chronic 1 Stable Condition)
163004Z	79	F	PD	Cerebral infarction	600 mg	580/3	Moderate	Unlikely	Yes	Resolved
168004A	62	M	PD	Dehydration	600 mg	477/ND	Severe	Not related	Yes	Ongoing
171008	82	F	PD	Malignant hypertension	400 mg	537/4	Severe	Unlikely	Yes	Resolved
172002Z[4]	67	M	PD	Dizziness	400 mg	ND/ND	Moderate	Not related	No	Ongoing
172003Z	59	F	PD	Nausea	100 mg	2/25	Moderate	Probably	No	Resolved
175001Z	67	F	PD	Fall	400 mg	38/ND	Severe	Unlikely	No	Ongoing
176001Z	85	F	PD	Aortic stenosis	600 mg	377/ND	Moderate	Unlikely	Yes	Ongoing

Patient #	Age	Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Day on Study [1]/ Duration (days)	Severity	Relationship	SAE	Outcome
179002	49	F	PD	Altered state of consciousness	200 mg	103/6	Severe	Unlikely	Yes	Resolved with sequelae
179003Z	80	M	PD	Dizziness	400 mg	64/ND	Moderate	Not related	No	Ongoing
300005	73	F	PAF	Transient ischemic attack	600 mg	329/1	Mild	Unlikely	Yes	Resolved
404002	70	M	MSA	Hypertensive crisis	600 mg	105/2	Severe	Probably	Yes	Resolved
501003	55	F	MSA	Atrial fibrillation	500 mg	34/18	Severe	Unlikely	Yes	Resolved
503004	60	F	MSA	Pneumonia	300 mg	169/17	Severe	Possibly	Yes	Death
514001	59	M	PD	Suicide attempt	500 mg	169/1	Severe	Possibly	Yes	Resolved
514003	55	F	PD	Myalgia	200 mg	19/19	Moderate	Probably	No	Resolved
Study 306										
156006 [5]	76	F	PD	Abdominal discomfort	200 mg	9/NA	Moderate	Not related	No	Ongoing
				Vision blurred	200 mg	9/6	Moderate	Not related	No	Resolved
				Dizziness	200 mg	9/6	Moderate	Possibly	No	Resolved
				Headache	200 mg	9/13	Moderate	Not related	No	Resolved
				Benign neoplasm of bladder	200 mg	11/NA	Mild	Not related	No	Ongoing
				Cholelithiasis	200 mg	11/NA	Mild	Not related	No	Ongoing
146006	62	Male	PD	Syncope	Placebo	33/1	Moderate	Not related	Yes	Resolved
160005	76	Female	PD	BP increased	Placebo	5/1	Moderate	Possibly	No	Resolved
160006	84	Male	PD	Hypertension	Placebo	19/NA	Severe	Probably	No	Ongoing
161005	81	Female	PD	Malaise	Placebo	2/NA	Moderate	Unlikely	No	Ongoing
176003	82	Female	PD	Gastroenteritis	Placebo	8/4	Moderate	Possibly	No	Resolved
110006 [6]	77	Male	PD	Atrial fibrillation	300 mg	12/76	Moderate	Probably	Yes	Resolved
115004	78	Male	PD	Hallucination	200 mg	10/1	Moderate	Possibly	No	Resolved
131005	79	Male	PD	Hypertension	600 mg	20/NA	Mild	Not related	No	Ongoing
132004	81	Female	PD	Hypertension	100 mg	5/22	Mild	Definitely	No	Resolved
141004	68	Male	PD	Abnormal dreams	100 mg	19/24	Mild	Probably	No	Resolved
152004	77	Male	PD	Hypotension	400 mg	15/NA	Moderate	Possibly	No	Ongoing
156002	69	Male	PD	Blood pressured increased	100 mg	1/NA	Moderate	Possibly	No	Ongoing
156007	76	Male	PD	Mental status changes	400 mg	20/1	Moderate	Possibly	Yes	Resolved
160003	74	Male	PD	Blood pressure increased	300 mg	20/NA	Severe	Probably	No	Ongoing
182008	76	Male	PD	Parkinson’s disease	500 mg	5/NA	Moderate	Unlikely	No	Ongoing
184003	79	Female	PD	Hypertension	300 mg	5/4	Severe	Definitely	Yes	Resolved

AE=adverse event; BP=blood pressure; F=female; M=male; MSA=Multiple System Atrophy; ND=not determined; NDAN=Non-Diabetic Autonomic Neuropathy; OL=open-label; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; PI=Principal Investigator; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TID=three times daily.

Note: Due to the titration design of the studies, adjustments to doses as allowed in the protocols, and up-titration occurring in the evening after a study visit with assessments at the previous dose, determining a patient's exact dose can be problematic for some patients. These tables represent the best estimate of dose at time of event drawn from per patient listings of study medication, visit dates, adverse events, and titration visits.

1 Study day equals day of onset of AE minus first day of treatment +1.

2 In Patient 402005, the event of renal failure acute did not resolve, it worsened to chronic renal failure.

3 Patient ID numbers were unique to individual studies, not to the entire development program, and duplication of patient ID numbers exist. To prevent confusion, patients who entered Study 304 from Study 303 are marked with an "A" at the end of their patient ID and patients from Study 306 were marked with a "Z". Caution should be exercised when aggregating data across studies given the potential for miscounting of subjects.

4 Patient 101010A discontinued Study 304 due to an AE of "mild peripheral neuropathy" and Patient 172002Z discontinued Study 304 due to an AE of "worsening of dizziness." The dates of onset of these AEs were reported as being prior to these patients' start dates in Study 304. Patient 101010A had been taking 500 mg TID in Study 303 at the time of the event. Patient 172002Z had been taking 400 mg TID in Study 306 at the time of the event.

5 None of these 6 TEAEs was determined to be the primary reason the patient discontinued from the study; therefore, the official reason the patient was discontinued from Study 306A was "Other" ("Patient and PI felt it would be best for her to stop study drug due to all the problems the patient was having").

6 Patient was randomized to the placebo group, but was mistakenly treated with droxidopa for 3 days

10.7 Appendix 7: Listing of TEAEs Related to Elevations in Blood Pressure by Study

This appendix includes all TEAEs related to elevations in BP captured in the databases of Studies 301, 302, 303, 304, and 306.

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event/ Study Phase	Severity	Relationship	SAE	Drug Action [1]	Outcome	Other Potentially Relevant AEs
Study 301										
106003	64/M	PD	Hypertension	100 mg / OL	Mild	Probably	No	Disc	Resolved without treatment	None
162002	62/M	MSA	Hypertension	600 mg / OL	Mild	Possibly	No	Decr	Resolved without treatment	Headache
162003	75/M	PAF	Hypertension	600 mg / DB	Mild	Possibly	No	None	Resolved without treatment	Headache
162004	59/F	MSA	Hypertension	600 mg / OL	Mild	Possibly	No	Decr	Resolved without treatment	Headache, blurred vision
163004	67/M	PD	Hypertension	0 mg / Washout	Mild	Not related	No	None	Resolved without treatment	Dizziness
171002	66/M	PD	Hypertension	500 mg / OL[2]	Mild	Probably	No	None	Ongoing	Headache
400002	65/M	PD	Hypertension	200 mg / DB	Moderate	Probably	No	Inter	Resolved without treatment	Dizziness
400004	53/M	MSA	Hypertension	200 mg / OL	Mild	Probably	No	Disc	Resolved without treatment	None
504001	52/F	MSA	BP increased	600 mg / OL	Mild	Not related	No	Decr	Resolved without treatment	Headache
511001	40/M	PAF	BP increased	300 mg / OL	Moderate	Possibly	No	Disc	Resolved with treatment	None
Study 302										
105001	54/M	MSA	Hypertension	100 mg/ OL	Moderate	Definitely	No	Disc	Resolved without treatment	None
113003	60/M	PAF	Hypertension	600 mg/ OL	Moderate	Possibly	No	None	Resolved without treatment	Chest pain
121003	24/F	PAF	Hypertension	200 mg/ OL	Mild	Probably	No	Inter	Resolved without treatment	Headache, Chest pain

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event/ Study Phase	Severity	Relationship	SAE	Drug Action [1]	Outcome	Other Potentially Relevant AEs
Study 303										
134005	83/F	PD	Hypertension	200 mg / OL	Moderate	Possibly	No	Disc	Resolved with treatment	None
145001	75/M	PAF	Hypertension	Placebo / DB	Mild	Unlikely	No	None	Ongoing	Dizziness
Study 304 [3]										
100007	77/M	PAF	Hypertensive crisis	600 mg	Moderate	Unlikely	Yes	Disc	Resolved with treatment	None
103001	61/M	MSA	Hypertension	500 mg / OL	Mild	Unlikely	No	None	Ongoing	Headache (verbatim term: "pounding in head")
103004	76/M	PAF	Hypertension	600 mg / OL	Moderate	Probably	No	Decr	Resolved	None
105002	67/M	MSA	Hypertension	600 mg / OL	Mild	Possibly	No	Decr	Ongoing	Pain (verbatim term: "pain, increasing generalized")
			Hypertension	600 mg / OL	Moderate	Probably	No	Decr	(none listed)	None
105010	66/M	PAF	Hypertension	600 mg / OL	Mild	Possibly	No	None	Resolved without treatment	None
			Hypertension	400 mg / OL	Moderate	Possibly	No	Decr	Resolved without treatment	None
106001A	86/F	PD	Hypertension	500 mg / OL	Mild	Possibly	No	Decr	Ongoing	None
113003Z	72/M	PD	Hypertension	600 mg / OL	Moderate	Unlikely	No	None	Ongoing	Deep vein thrombosis; venous thrombosis; venous thrombosis limb; edema peripheral; OH
118005Z	80/M	PD	Hypertension	100 mg / OL	Moderate	Unlikely	No	None	Resolved without treatment	Chest pain
			Hypertension	100 mg / OL	Mild	Possibly	Yes	None	Resolved with treatment	Non-cardiac chest pain
129003A	77/M	PD	Hypertension	100 mg / OL	Mild	Probably	No	Decr	Ongoing	None
132007Z	81/M	PD	Hypertension	400 mg / OL	Mild	Probably	No	Inter	Resolved without treatment	None
132011Z	66/M	PD	Hypertension	600 mg / OL	Mild	Probably	No	Decr	Resolved without treatment	None
137002Z	71/M	PD	Hypertension	100 mg / OL	Severe	Definitely	Yes	Disc	Resolved with treatment	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event/ Study Phase	Severity	Relationship	SAE	Drug Action [1]	Outcome	Other Potentially Relevant AEs
179001	63/M	PD	Hypertension	600 mg / OL	Moderate	Probably	No	Decr	Resolved without treatment	None
			Hypertension	500 mg / OL	Moderate	Probably	No	None	Resolved without treatment	None
181001Z	75/M	PD	Hypertension	100 mg / OL	Moderate	Possibly	No	None	Ongoing	Altered state of consciousness, Blurred vision, Chest discomfort, Chills, Headache, Tremor, Vertigo
183001Z	74/M	PD	Hypertension	300 mg / OL	Mild	Probably	No	None	Resolved without treatment	None
503002	57/F	MSA	Hypertension	300 mg / OL	Mild	Probably	No	Decr	Ongoing	None
506005	75/M	MSA	Hypertension	400 mg / OL	Mild	Possibly	No	Decr	Resolved without treatment	None
507002	30/F	NDAN	Hypertension	400 mg / OL	Moderate	Possibly	No	None	Resolved without treatment	None
171008	82/F	PD	Malignant hypertension	400 mg / OL	Severe	Unlikely	Yes	Disc	Resolved with treatment	Encephalopathy; confusional state
100007	77/M	PAF	Hypertensive crisis	600 mg / OL	Moderate	Unlikely	Yes	Disc	Resolved with treatment	None
305003	59/M	MSA	Hypertensive crisis	200 mg / OL	Mild	Possibly	No	Decr	Resolved without treatment	None
404002	70/M	MSA	Hypertensive crisis	600 mg / OL	Severe	Probably	Yes	Disc	Resolved with treatment	None
117004	60/M	PD	BP increased (verbatim term: “elevated supine blood pressure”)	600 mg / OL	Mild	Probably	No	None	Resolved without treatment	Blurred vision
122004A	80/M	PD	BP increased (verbatim term: “elevated blood pressure ‘intermittent’”)	500 mg / OL	Moderate	Unlikely	No	Disc	Ongoing	None
126001Z	79/F	PD	BP increased	300 mg / OL	Moderate	Not Related	No	Decr	Resolved with treatment	Asthenia, palpitations
141002Z	79/M	PD	BP increased	500 mg / OL	Mild	Possibly	No	Decr	Resolved without treatment	None
162002	62/M	MSA	BP increased	500 mg / OL	Mild	Probably	No	Decr	Resolved without treatment	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event/ Study Phase	Severity	Relationship	SAE	Drug Action [1]	Outcome	Other Potentially Relevant AEs
108002A	78/F	MSA	BP increased	600 mg / OL	Mild	Possibly	No	Decr	Resolved	None
503004	60/F	MSA	BP increased	600 mg / OL	Moderate	Definitely	No	Decr	Resolved without treatment	None
			BP increased	400 mg / OL	Moderate	Definitely	No	Decr	Resolved without treatment	
134001A	88/F	MSA	Blood pressure fluctuation	400 mg TID	Severe	Unlikely	Yes	None	Ongoing with treatment	None
Study 306										
118001	89/F	PD	BP increased	600 mg / DB	Mild	Not related	No	None	Resolved without treatment	None
			BP increased	600 mg / DB	Mild	Not related	No	None	Resolved without treatment	Visual impairment
102003	75/F	PD	BP increased	Placebo / DB	Mild	Not related	No	None	Resolved without treatment	None
163003	74/F	PD	BP increased	Placebo / DB	Mild	Probably	No	Decr	Resolved without treatment	None
106001	67/F	PD	Hypertension [4]	300 mg/ DB	Moderate	Definitely	No	Decr	Ongoing	Headache
113002	72/F	PD	Hypertension [4]	100 mg / DB	Mild	Probably	No	None	Resolved	None
			Hypertension [4]	600 mg / DB	Mild	Probably	No	None	Resolved	None
			Hypertension [4]	600 mg / DB	Mild	Probably	No	Decr	Resolved	None
131005	79/M	PD	Hypertension	600 mg / DB	Mild	Not related	No	Disc	Ongoing	None
132004	81/F	PD	Hypertension [4]	100 mg / DB	Mild	Definitely	No	Disc	Resolved	None
137002	71/M	PD	Hypertension [4]	600 mg / DB	Mild	Possibly	No	None	Resolved	None
141005	77/M	PD	Hypertension	500 mg / DB	Moderate	Possibly	No	Decr	Resolved	None
			Hypertension	400 mg / DB	Moderate	Possibly	No	None	Resolved	
156006	76/F	PD	Hypertension	200 mg / DB	Moderate	Possibly	No	None	Ongoing	Vision blurred, Headache
184003	79/F	PD	Hypertension [5]	300 mg / DB	Severe	Definitely	Yes	Disc	Resolved	Headache
160006	84/M	PD	Hypertension	Placebo / DB	Severe	Probably	No	Decr	Resolved	None
			Hypertension	Placebo / DB	Severe	Probably	No	Disc	Ongoing	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event/ Study Phase	Severity	Relationship	SAE	Drug Action [1]	Outcome	Other Potentially Relevant AEs
139001	68/F	PD	BP increased	200 mg / DB	Mild	Possibly	No	None	Resolved	None
			BP increased	400 mg / DB	Moderate	Possibly	No	Decr	Resolved	None
			BP increased	300 mg / DB	Mild	Possibly	No	None	Resolved	None
			BP increased	300 mg / DB	Moderate	Possibly	No	Decr	Resolved	None
			BP increased	200 mg / DB	Mild	Possibly	No	None	Resolved	None
156002	69/M	PD	BP increased	100 mg / DB	Moderate	Possibly	No	Disc	Ongoing	None
160003	74/M	PD	BP increased	300 mg / DB	Severe	Probably	No	Disc	Ongoing	None
118005	79/M	PD	BP increased	Placebo / DB	Moderate	Definitely	No	Decr	Resolved	Flushing; Hot flush
139002	62/M	PD	BP increased	Placebo / DB	Mild	Possibly	No	None	Resolved	None
160005	76/F	PD	BP increased	Placebo / DB	Moderate	Possibly	No	Disc	Resolved	None
162002	71/F	PD	BP increased	Placebo / SFU	Moderate	Not related	No	None	Resolved	None
178003	74/F	PD	BP increased	Placebo / DB	Moderate	Not related	No	None	Resolved	None
118003	69/M	PD	BP systolic increased	400 mg / DB	Mild	Possibly	No	None	Resolved	None
111003	69/M	PD	BP systolic increased	600 mg / DB	Moderate	Probably	No	Decr	Resolved	None

AE=adverse event; BP=blood pressure; DB=Double-blind Phase; Decr=decreased; Disc=discontinued; F=female; M=male; MSA=Multiple System Atrophy; N/A=not applicable; ND=not determined; NDAN=Non-diabetic Autonomic Neuropathy; OL=Open-label Phase; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; SAE=serious adverse event; SFU=safety follow-up; TID=three times daily.

Note: Due to the titration design of the studies, adjustments to doses as allowed in the protocols, and up-titration occurring in the evening after a study visit with assessments at the previous dose, determining a patient's exact dose can be problematic for some patients. These tables represent the best estimate of dose at time of event drawn from per patient listings of study medication, visit dates, adverse events, and titration visits.

* Patient has more than 1 AE that occurred at different doses.

1 Drug action taken: disc=study drug discontinued; incr=study drug dose increased; inter=study drug interrupted; none=no interruption of study drug.

2 AE for Study 301 was captured at the follow-up call; patient had already enrolled in Study 303 and was taking 500 mg OL droxidopa.

3 Patient ID numbers were unique to individual studies, not to the entire development program, and duplication of patient ID numbers exist. To prevent confusion, patients who entered Study 304 from Study303 are marked with an "A" at the end of their patient ID and patients from Study 306 were marked with a "Z". Caution should be exercised when aggregating data across studies given the potential for miscounting of subjects.

4 Raw term indicated event associated with supine hypertension.

5 Raw term indicated worsening of/exacerbation of hypertension.

10.8 Appendix 8: Listing of Cardiovascular-related TEAEs by Study

This appendix includes all cardiovascular-related TEAEs captured in the databases of Studies 301, 302, 303, 304, and 306.

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
Study 301											
124006	71/M	PAF	Palpitations	300 mg/ OL	3/ 1	Moderate	Possibly	No	Disc	Resolved without treatment	None
501007	57/F	PD	Palpitations	600 mg/ OL	9/ 1	Mild	Possibly	No	None	Resolved without treatment	None
			Palpitations	600 mg/ OL	9/ 1	Mild	Possibly	No	None	Resolved without treatment	
			Palpitations	600 mg/ OL	10/ 1	Mild	Possibly	No	None	Resolved without treatment	
607002	59/F	PD	Palpitations	200 mg/ OL	3/ 2	Moderate	Probably	No	None	Resolved without treatment	None
103009 [3]	82/M	NDAN	Palpitations	300 mg/ OL	4/ 6	Mild	Unlikely	No	None	Resolved without treatment	Headache, Hypertension
500002	28/F	PAF	Palpitations	200 mg/ OL	4/ 1	Mild	Possibly	No	None	Resolved without treatment	None
512002	29/F	PAF	Atrioventricular block first degree	0 mg/ OL Washout	10/ ND	Mild	Probably	No	None	Resolved without treatment	Headache
509005	24/M	PAF	Atrioventricular block first degree	300 mg/ OL	12/ 7	Mild	Not related	No	None	Resolved without treatment	None
607001	74/M	PD	Supraventricular extrasystoles	0 mg/ OL Washout	13/ 11	Mild	Unlikely	No	None	Resolved without treatment	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
Study 302											
104003	83/M	PD	Palpitations	100 mg/ OL	4/ 1	Mild	Possibly	No	None	Resolved without treatment	Nervousness
114003 [4]	63/F	MSA	Cardiopulmonary Arrest [4]	N/A - Discontinued	13/2	ND	Not related	Yes	N/A	Death	None
123003	69/M	PAF	Palpitations	200 mg/ OL	3/ 1	Mild	Possibly	No	None	Resolved without treatment	Dizziness, dysarthria, asthenia, worsened dizziness
300004	76/F	MSA	Palpitations	300 mg/ OL	6/ 1	Mild	Possibly	No	None	Resolved without treatment	Atrioventricular block 1st degree (ongoing; non-treatment emergent), asthenia
402003	69/F	PD	Palpitations	200 mg/ OL	15/ 3	Mild	Possibly	No	Disc	Resolved without treatment	Hyperhidrosis (2 events), muscle rigidity
401001	49/F	MSA	Palpitations	600 mg/ OL	9/ 1	Mild	Probably	No	Decr	Resolved without treatment	Feeling abnormal, dyspnea
101007	79/F	PAF	Atrial flutter	300 mg/ OL	22/ ND	Mild	Unlikely	No	Disc	Ongoing	None
			Chest pain (secondary to RV pacing)	300 mg/ OL	22/ ND	Mild	Not related	No	None	Ongoing	
113003	60/M	PAF	Chest pain	600mg/ OL	14/ 1	Moderate	Unlikely	No	None	Resolved without treatment	Hypertension
121003	24/F	PAF	Chest pain	300 mg/ OL	3/ 2	Mild	Probably	No	Decr	Resolved without treatment	Headache, hypertension
502005	30/F	Other	Chest pain (associated with dysautonomia)	500 mg/ OL	11/ 3	Moderate	Unlikely	No	Incr	Resolved without treatment	None
122003	67/M	PD	Angina Pectoris	100 mg/ OL	1/ 1	Moderate	Not related	No	Disc	Resolved with treatment	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
130003	77/M	PD	Coronary artery disease	100 mg/ OL	8/ ND	Moderate	Not related	Yes	Disc	Ongoing	None
200005	86/M	PAF	Cardiac failure congestive	100 mg/ OL	6/ 29	Moderate	Not related	Yes	None	Resolved with treatment	Iron deficiency anemia, mixed dementia, pneumonia
Study 303											
106001	85/F	PD	Supraventricular extrasystoles	100 mg/ OL	33/ 167	Mild	Possibly	No	None	Resolved without treatment	None
			Atrioventricular block first degree	200 mg/ DB	88/ 14	Mild	Unlikely	No	None	Resolved without treatment	
			Atrial fibrillation	200 mg/ LTFU	200/ 68	Moderate	Possibly	Yes	None	Resolved without treatment	
			Supraventricular extrasystoles	200 mg/ LTFU	284/ ND	Mild	Possibly	No	None	Ongoing	
			Atrioventricular block first degree	400 mg/ LTFU	523/ ND	Mild	Unlikely	No	None	Ongoing	
106004	78/M	Other	Supraventricular extrasystoles	400 mg/ LTFU	364/ ND	Mild	Possibly	No	None	Ongoing	None
108002	76/F	MSA	Angina pectoris	400 mg/ OL	36/ 1	Mild	Possibly	No	None	Resolved with treatment	None
113003	60/M	PAF	Angina pectoris	600 mg/ OL	1/ 2	Moderate	Unlikely	No	None	Resolved with treatment	Catheterization cardiac, stent placement
			Angina pectoris	500 mg/ OL	91/ 2	Moderate	Unlikely	Yes	Inter	Resolved with treatment	
129002	63/F	MSA	Sudden cardiac death	200 mg/ LTFU	286/ 1	Severe	Not related	Yes	None	Death	None
134001	86/F	MSA	Bundle branch block left	200 mg/ DB	84/ ND	Mild	Possibly	No	None	Ongoing	None
			Atrial fibrillation	400 mg/ LTFU	397ND	Mild	Unlikely	No	None	Ongoing	
134004	73/M	PD	Cardiomegaly	300 mg/ LTFU	201/ ND	Mild	Unlikely	No	None	Ongoing	Bronchial hemorrhage, nausea

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
134005	83/F	PD	Coronary artery disease	200 mg/ LTFU	212/ 2	Severe	Not related	Yes	None	Resolved with treatment	None
136001	57/M	PD	Tachycardia	Off Drug [5]/ LTFU	226/ ND	Moderate	Not related	No	None	Ongoing	None
136002	81/F	PD	Ventricular extrasystoles	400 mg/ DB	97/ 90	Mild	Unlikely	No	None	Resolved without treatment	Dizziness, Asthenia, Vertigo
			Sinus bradycardia	200 mg/ LTFU	102/ ND	Mild	Unlikely	No	None	Ongoing	
			Ventricular extrasystoles	200 mg/ LTFU	187/ 86	Mild	Unlikely	No	None	Resolved without treatment	
145001	75/M	PAF	Angina pectoris	100 mg/ LTFU	290/ 4	Severe	Not related	Yes	Inter	Resolved without treatment	Coronary artery stent insertion
163001	73/M	PAF	Chest pain	500 mg/ LTFU	172/ 99	Mild	Not related	No	None	Resolved without treatment	None
			Chest pain	500 mg/ LTFU	327/ 1	Mild	Not related	No	None	Resolved without treatment	
204002	73/M	PD	Ventricular extrasystoles	200 mg/ OL	1/ ND	Mild	Probably	No	None	Ongoing	None
			Conduction disorder	200 mg/ OL	28/ ND	Moderate	Probably	No	None	Ongoing	
			Ventricular extrasystoles	200 mg/ OL	28/ ND	Moderate	Probably	No	Disc	Ongoing	
401010	71/M	PD	Atrioventricular block first degree	300 mg/ OL	36/ ND	Mild	Possibly	No	None	Ongoing	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
401013	53/M	PD	Atrioventricular block first degree	200 mg/ OL	1/ 22	Mild	Possibly	No	None	Resolved without treatment	None
			Bundle branch block left	200 mg/ OL	1/ ND	Mild	Not related	No	None	Ongoing	
			Atrioventricular block first degree	200 mg/ OL	77/ 27	Mild	Possibly	No	None	Resolved without treatment	
			Chest pain	200 mg/ LTFU	257/ 5	Mild	Probably	No	Inter	Resolved without treatment	
			Chest pain	200 mg/ LTFU	265/ 11	Moderate	Possibly	No	Disc	Resolved without treatment	
406001	68/F	PD	Arrhythmia	200 mg/ OL	30/ 58	Moderate	Possibly	No	Decr	Resolved with treatment	Hypoesthesia, syncope
Study 304 [6]											
100006	76/M	PAF	Chest discomfort	600 mg	913/ 5	Moderate	Unlikely	Yes	None	Resolved with treatment	Dyspnea
			Aortic aneurysm	600 mg	513/ 2	Moderate	Not related	Yes	None	Resolved with treatment	None
100007	77/M	PAF	Hypertensive crisis	600 mg	104/ 17	Moderate	Unlikely	Yes	Disc	Resolved with treatment	None
103006	73/M	NDAN	Ventricular extrasystoles	400 mg	408/ 2	Mild	Unlikely	No	None	Resolved without treatment	None
			AV block first degree	400 mg	639/ ND	Mild	Not related	No	None	Ongoing	
			Sinus bradycardia	400 mg	639/ ND	Mild	Not related	No	None	Ongoing	
104001A	85/M	MSA	Atrial fibrillation	600 mg	462 / ND	Mild	Possibly	No	None	Ongoing	None
105007	56/F	MSA	Circulatory Collapse	500 mg	128/1	Moderate	Not related	Yes	Disc	Death	Pneumonia, sepsis

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
106001A	86/F	PD	Supraventricular extrasystoles	0 mg	-256 / ND	Mild	Possibly	No	None	Ongoing	Elevated CK-MB, hypertension
106004A	79/M	Other	Supraventricular extrasystoles	0 mg	-115/ 99	Mild	Possibly	No	None	Resolved without treatment	None
113003A	62/M	PAF	Angina pectoris	600 mg	20/ 1	Moderate	Unlikely	No	None	Resolved with treatment	None
			Myocardial infarction	600 mg	550/ 1	Severe	Not related	Yes	Disc	Death	Loss of consciousness
113005A	73/M	MSA	AV block first degree	0 mg	-609/ ND	Mild	Unlikely	No	None	Ongoing	None
115004A	75/M	NDAN	Myocardial infarction	400 mg	363 / 1	Severe	Possibly	Yes	Disc	Death	Pleural effusion, pneumonia, neutropenia
117001	75/M	PD	Atrial flutter	500 mg	81/ 1	Mild	Not related	No	None	Resolved with treatment	Anxiety, dyspnea, worsening orthostatic hypotension
117007	75/M	PD	Atrial tachycardia	500 mg	88/ 1	Moderate	Not related	No	None	Resolved with treatment	None
			Chest discomfort	500 mg	88/ ND	Mild	Not related	No	None	Ongoing	
			Atrial flutter	500 mg	116/ 1	Moderate	Possibly	Yes	None	Resolved with treatment	
			Atrial fibrillation	500 mg	117/ ND	Mild	Possibly	No	None	Ongoing	
118005Z	80/M	PD	Chest pain	100 mg	74/ 2	Severe	Unlikely	Yes	Inter	Resolved with treatment	Hypertension
124001	74/M	PAF	Atrial fibrillation	500 mg	665/ ND	Moderate	Not related	No	None	Ongoing	Syncope
125010	80/M	PD	Cardio-respiratory arrest	600 mg	37/ 2	Severe	Unlikely	Yes	Disc	Death	None
126001Z	79/F	PD	Palpitations	300 mg	432/ 1	Moderate	Not related	No	None	Resolved with treatment	Headache, vertigo, nausea, BP increased, asthenia
126009	79/M	PD	Supraventricular tachycardia	600 mg	579 / 6	Moderate	Not related	Yes	Inter	Resolved with treatment	Pneumonia aspiration
132008Z	80/M	PD	Bradycardia	600 mg	84/ ND	Moderate	Unlikely related	No	None	Ongoing	Fall

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
132017Z	78/M	PD	Cardiac failure congestive	300 mg	244 / 3	Mild	Unlikely related	Yes	Disc	Resolved without treatment	Dizziness, nausea
137002Z	71/M	PD	Supraventricular extrasystoles	0 mg	-28 / ND	Mild	Not related	No	None	Ongoing	Hypertension
145001Z	78/M	PD	Cardio-respiratory arrest	200 mg	104 / 1	Severe	Unlikely related	Yes	Disc	Death	Peridiverticular abscess, dehydration, hypovolemia, diarrhea
146003A	82/F	PD	Bradycardia	600 mg	124/ 15	Moderate	Not related	Yes	Inter	Resolved with treatment	Acute respiratory failure, aspiration, respiratory failure
146004A	83/F	PD	Cardiac arrest	600 mg	530/ 1	Severe	Not related	Yes	Disc	Death	Hip fracture
163003Z	74/F	PD	Atrial fibrillation	200 mg	87/ 4	Moderate	Unlikely related	Yes	None	Resolved with treatment	Syncope
171008	82/F	PD	Malignant Hypertension	400mg	537/ 4	Severe	Unlikely related	Yes	Disc	Resolved with treatment	Encephalopathy, confusional state
181001Z	75/M	PD	Bradycardia	0 mg	-48/ 653	Moderate	Possibly	No	None	Resolved without treatment	None
			Sinus bradycardia	0 mg	-48/ ND	Moderate	Possibly	No	None	Ongoing	
			Chest discomfort	100 mg	1/ 1	Mild	Possibly	No	Inter	Resolved without treatment	Vision blurred, altered state of consciousness, chills, headache, hypertension, tremor, vertigo
			Chest pain	200 mg	283/ 1	Mild	Not related	No	None	Resolved without treatment	Disorientation, contusion, excoriation, skin laceration
305003	59/M	MSA	Hypertensive crisis	200 mg	1/ 1	Mild	Possibly	No	Decr	Resolved without treatment	None
404002	70/M	MSA	Hypertensive crisis	600 mg	105/ 1	Severe	Probably	Yes	Disc	Resolved with treatment	None
501003	55/F	MSA	Atrial fibrillation	500 mg	34/ 18	Severe	Unlikely	Yes	Disc	Resolved with treatment	None

Patient #	Age/ Gender	Prim. Diag.	Preferred Term	Dose (TID) at Time of Event	Study Day of onset [1]/ Duration (days)	Severity	Relationship	SAE	Drug Action [2]	Outcome	Other Potentially Relevant AEs
501007	57/F	PD	Palpitations	500 mg	7/ 13	Mild	Possibly	No	Decr	Resolved without treatment	None
			Palpitations	400 mg	29/ 9	Mild	Possibly	No	Inter	Resolved without treatment	
507004	55/M	PD	Tachycardia	300 mg	26/ 37	Mild	Unlikely	No	None	Resolved with treatment	None
Study 306											
178001	69/M	PD	Sinus bradycardia	Placebo	71/ 12	Mild	Possibly	No	None	Resolved without treatment	None
181001	74/M	PD	Sinus bradycardia	500 mg	20/ ND	Moderate	Possibly	No	None	Ongoing	None
110006	77/M	PD	Atrial fibrillation	Placebo [7]	12/ 76	Moderate	Probably	Yes	Disc	Resolved with treatment	None
132021	79/M	PD	Tachycardia	Placebo	2/ 3	Mild	Possibly	No	None	Resolved without treatment	None
132029	67/F	PD	Tachycardia	200 mg	7/ 59	Mild	Possibly	No	None	Resolved without treatment	None
137002	71/M	PD	Supraventricular extrasystoles	600 mg	45/ ND	Mild	Not related	No	None	Ongoing	Hypertension, headache
156007	76/M	PD	Tachycardia paroxysmal	400 mg	20/ 2	Mild	Not related	No	None	Resolved without treatment	Bronchial hyperreactivity, mental status changes, presyncope, dehydration

AE=adverse event; BP=blood pressure; DB=double-blind; F=female; LTFU=Long-term Follow-up; M=male; MSA=Multiple System Atrophy; ND=not determined; NDAN=Non-diabetic Autonomic Neuropathy; OL=Open-label; OST=Orthostatic Standing Test; PAF=Pure Autonomic Failure; PD=Parkinson's Disease; TEAE=treatment-emergent adverse event; TID=three times daily.

Note: Due to the titration design of the studies, adjustments to doses as allowed in the protocols, and up-titration occurring in the evening after a study visit with assessments at the previous dose, determining a patient's exact dose can be problematic for some patients. These tables represent the best estimate of dose at time of event drawn from per patient listings of study medication, visit dates, adverse events, and titration visits.

1 Study day equals day of onset of AE minus first day of treatment +1.

2 Drug action taken: disc=study drug discontinued; incr=study drug dose increased; inter=study drug interrupted; none=no interruption of study drug.

3 Patient 103009 in Study 301was diagnosed at screening with ongoing hypertensive episodes. These eventually led to discontinuation, which coincided with the AE of palpitations and headache, but as the hypertension was not treatment emergent, the patient is not included in the hypertensive AE table or narratives or in the narrative of cardiac AEs leading to discontinuation. The patient continued to have elevated blood pressure during the OST at both 7 and 19 days following drug discontinuation.

4 One death in Study 302 (Patient 114003) occurred outside the pre-defined 7 day follow up period, so was not captured in the study database; information from the CIOMS is included here.

5 Patient 136001 in Study 303 interrupted droxidopa treatment for ~2 months due to an SAE. The TEAE of tachycardia started while off drug and was ongoing when therapy with 100mg droxidopa was resumed.

6 Patient ID numbers were unique to individual studies, not to the entire development program, and duplication of patient ID numbers exist. To prevent confusion, patients who entered Study 304 from Study303 are marked with an "A" at the end of their patient ID and patients from Study 306 were marked with a "Z". Caution should be exercised when aggregating data across studies given the potential for miscounting of subjects.

7 Patient was randomized to placebo, but mistakenly received droxidopa for 3 days during titration, returned to placebo for 3 days, then reported the TEAE of atrial fibrillation.

10.9 Appendix 9: Clinical Global Impressions Analyses

Table 10-11 Study 301: Summary of Clinical Global Impressions-Severity (FAS, LOCF)

	Placebo (N=80) n (%)	**Droxidopa** (N=82) n (%)	**p-value**[1]
Clinician-rated Severity			
Randomization			
Normal: Borderline nOH	6 (7.5)	5 (6.1)	
Mild: Moderate nOH	46 (57.5)	48 (58.5)	
Marked nOH: Most Ill with nOH	28 (35.0)	29 (35.4)	
End of Study			0.534
Normal: Borderline nOH	15 (18.8)	21 (25.6)	
Mild: Moderate nOH	44 (55.0)	39 (47.6)	
Marked nOH: Most Ill with nOH	21 (26.3)	22 (26.8)	
Improvement by at Least 1 Point from Randomization to End of Study	27 (33.8)	36 (43.9)	0.201
Patient-rated Severity			
Randomization			
Normal: Borderline nOH	4 (5.0)	6 (7.3)	
Mild: Moderate nOH	38 (47.5)	36 (43.9)	
Marked nOH: Most Ill with nOH	38 (47.5)	40 (48.8)	
End of Study			0.327
Normal: Borderline nOH	16 (20.0)	23 (28.0)	
Mild: Moderate nOH	47 (58.8)	39 (47.6)	
Marked nOH: Most Ill with nOH	17 (21.3)	20 (24.4)	
Improvement by at Least 1 Point from Randomization to End of Study	37 (46.3)	48 (58.5)	0.157

FAS=Full Analysis Set; LOCF=last observation carried forward; nOH=Neurogenic Orthostatic Hypotension.

1 The p-values were from Fisher's exact test comparing distribution of droxidopa responses to placebo responses at End of Study.

Table 10-12 Study 301: Summary of Clinical Global Impressions-Improvement (FAS, LOCF)

	Placebo (N=80) n (%)	**Droxidopa** (N=82) n (%)	**p-value**[1]
Clinician-rated Improvement			
Randomization			
Very Much – Slightly Improved	42 (52.5)	32 (39.5)	
No Change	30 (37.5)	34 (42.0)	
Slightly Worse – Very Much Worse	8 (10.0)	15 (18.5)	
Not assessed	0	1	
End of Study			0.156
Very Much – Slightly Improved	51 (63.8)	62 (75.6)	
No Change	24 (30.0)	14 (17.1)	
Slightly Worse – Very Much Worse	5 (6.3)	6 (7.3)	
Not assessed	0	0	
Patient-rated Improvement			
Randomization			
Very Much – Slightly Improved	36 (45.6)	38 (46.9)	
No Change	19 (24.1)	22 (27.2)	
Slightly Worse – Very Much Worse	24 (30.4)	21 (25.9)	
Not assessed	1	1	
End of Study			0.081
Very Much – Slightly Improved	52 (65.0)	61 (75.3)	
No Change	21 (26.3)	10 (12.3)	
Slightly Worse – Very Much Worse	7 (8.8)	10 (12.3)	
Not assessed	0	1	

FAS=Full Analysis Set; LOCF=last observation carried forward.

1 The p-values were from Fisher's exact test comparing distribution of droxidopa responses to placebo responses at End of Study.

Table 10-13 Study 302: Summary of Clinical Global Impressions-Severity (FAS, LOCF)

	Placebo (N=51) n (%)	**Droxidopa** (N=50) n (%)	**p-value[1]**
Clinician-rated Severity			
Randomization			
Normal: Borderline nOH	9 (17.6)	12 (24.0)	
Mild: Moderate nOH	30 (58.8)	28 (56.0)	
Marked OH: Most Ill with nOH	12 (23.5)	10 (20.0)	
End of Study			
Normal: Borderline nOH	10 (19.6)	11 (22.0)	0.052
Mild: Moderate nOH	15 (29.4)	25 (50.0)	
Marked nOH: Most Ill with nOH	26 (51.0)	14 (28.0)	
Patient-rated Severity			
Randomization[2]			
Normal: Borderline nOH	22 (43.1)	18 (36.7)	
Mild: Moderate nOH	21 (41.2)	22 (44.9)	
Marked OH: Most Ill with nOH	8 (15.7)	9 (18.4)	
End of Study			
Normal: Borderline nOH	18 (35.3)	18 (36.0)	0.008
Mild: Moderate nOH	11 (21.6)	23 (46.0)	
Marked nOH: Most Ill with nOH	22 (43.1)	9 (18.0)	

FAS=Full Analysis Set; LOCF=last observation carried forward; nOH=Neurogenic Orthostatic Hypotension.
The p-values were from Fisher's exact test comparing distribution of droxidopa responses to placebo responses at End of Study.
One patient with Clinical Global Impressions-Severity not assessed at this visit is excluded from the in-text table.

Table 10-14 Study 302: Summary of Clinical Global Impressions-Improvement (FAS, LOCF)

	Placebo (N=51) n (%)	Droxidopa (N=50) n (%)	p-value[1]
Clinician-rated Improvement			
Randomization			
Very Much Improved	9 (17.6)	7 (14.0)	
Much improved	27 (52.9)	22 (44.0)	
Slightly Improved	12 (23.5)	19 (38.0)	
No Change	3 (5.9)	2 (4.0)	
Slightly Worse	0	0	
Much Worse	0	0	
Very Much Worse	0	0	
Not Assessed	0	0	
End of Study			
Very Much Improved	7 (14.3)	8 (16.0)	0.448
Much improved	12 (24.5)	15 (30.0)	
Slightly Improved	15 (30.6)	16 (32.0)	
No Change	4 (8.2)	5 (10.0)	
Slightly Worse	5 (10.2)	5 (10.0)	
Much Worse	5 (10.2)	0 (0.0)	
Very Much Worse	1 (2.0)	1 (2.0)	
Not Assessed	2	0	
Patient-rated Improvement			
Randomization			
Very Much Improved	14 (27.5)	13 (26.0)	
Much improved	23 (45.1)	17 (34.0)	
Slightly Improved	14 (27.5)	19 (38.0)	
No Change	0	1 (2.0)	
Slightly Worse	0	0	
Much Worse	0	0	
Very Much Worse	0	0	
Not Assessed	0	0	
End of Study			
Very Much Improved	8 (16.0)	10 (20.0)	0.384
Much improved	6 (12.0)	13 (26.0)	
Slightly Improved	19 (38.0)	14 (28.0)	
No Change	4 (8.0)	6 (12.0)	
Slightly Worse	5 (10.0)	4 (8.0)	
Much Worse	4 (8.0)	2 (4.0)	
Very Much Worse	4 (8.0)	1 (2.0)	
Not Assessed	1	0	

FAS=Full Analysis Set; LOCF=last observation carried forward.

1 The p-values were from Fisher's exact test comparing distribution of droxidopa responses to placebo responses at End of Study.

Table 10-15 Study 306B: Clinician- and Patient-Reported CGI-S Scores at Weeks 1, 2, 4, and 8 (FAS, MDE)

	Placebo (N=78)	Droxidopa (N=69)	Difference from Placebo (95% CI)	p-value[1]
Clinician-Reported CGI-S Scores				
Baseline				
N	77	69		
Mean (SD)	4.6 (0.94)	4.4 (0.95)		
Min, Max	3, 7	3, 6		
Week 1 (Visit 4)				
N	77	69		
Mean (SD)	3.5 (1.19)	3.0 (1.28)		
Min, Max	1, 6	1, 6		
Change from BL to Week 1 (Visit 4)				
N	77	69		
Mean (SD)	-1.1 (1.13)	-1.4 (1.28)	-0.4 (-0.7, 0.0)	0.025
Min, Max	-4, 1	-4, 1		
Week 2 (Visit 5)				
N	74	68		
Mean (SD)	3.6 (1.47)	3.0 (1.37)		
Min, Max	1, 7	1, 6		
Change from BL to Week 2 (Visit 5)				
N	74	68		
Mean (SD)	-1.0 (1.33)	-1.4 (1.44)	-0.4 (-0.9, 0.0)	0.036
Min, Max	-4, 2	-4, 1		
Week 4 (Visit 6)				
N	70	65		
Mean (SD)	3.5 (1.30)	3.2 (1.33)		
Min, Max	1, 6	0, 6		
Change from BL to Week 4 (Visit 6)				
N	70	65		
Mean (SD)	-1.1 (1.19)	-1.2 (1.61)	-0.1 (-0.6, 0.4)	0.362
Min, Max	-4, 1	-6, 3		
Week 8 (Visit 7)				
N	65	58		
Mean (SD)	3.7 (1.50)	3.3 (1.43)		
Min, Max	1, 7	1, 6		
Change from BL to Week 8 (Visit 7)				
N	65	58		
Mean (SD)	-0.9 (1.26)	-1.1 (1.33)	-0.2 (-0.7, 0.3)	0.295
Min, Max	-5, 1	-4, 2		

	Placebo (N=78)	Droxidopa (N=69)	Difference from Placebo (95% CI)	p-value[1]
Patient-Reported CGI-S Scores				
Baseline				
N	77	68		
Mean (SD)	4.4 (1.26)	4.3 (1.27)		
Min, Max	2, 7	1, 7		
Week 1 (Visit 4)				
N	77	69		
Mean (SD)	3.5 (1.27)	3.0 (1.32)		
Min, Max	1, 6	1, 6		
Change from BL to Week 1 (Visit 4)				
N	77	68		
Mean (SD)	-1.0 (1.52)	-1.2 (1.44)	-0.3 (-0.7, 0.2)	0.060
Min, Max	-6, 4	-5, 3		
Week 2 (Visit 5)				
N	74	68		
Mean (SD)	3.5 (1.25)	3.2 (1.37)		
Min, Max	0, 6	1, 6		
Change from BL to Week 2 (Visit 5)				
N	74	67		
Mean (SD)	-0.9 (1.55)	-1.0 (1.36)	-0.2 (-0.6, 0.3)	0.216
Min, Max	-4, 3	-4, 3		
Week 4 (Visit 6)				
N	72	65		
Mean (SD)	3.4 (1.30)	3.4 (1.39)		
Min, Max	0, 7	1, 7		
Change from BL to Week 4 (Visit 6)				
N	72	64		
Mean (SD)	-1.0 (1.59)	-0.9 (1.54)	0.2 (-0.4, 0.7)	0.896
Min, Max	-4, 4	-5, 3		
Week 8 (Visit 7)				
N	66	63		
Mean (SD)	3.5 (1.52)	3.4 (1.51)		
Min, Max	1, 6	1, 6		
Change from BL to Week 8 (Visit 7)				
N	66	62		
Mean (SD)	-0.9 (1.65)	-0.9 (1.66)	0.1 (-0.5, 0.6)	0.922
Min, Max	-5, 4	-5, 3		

ANCOVA=analysis of covariance; BL=Baseline; CGI-S=Clinical Global Impressions-Severity; CI=confidence interval; FAS=Full Analysis Set; Max=maximum; MDE=Missing data excluded; Min=minimum; SD=standard deviation.

1 Treatment differences tested using a parametric ANCOVA model with an effect for treatment and Baseline value.

Table 10-16 Study 306B: Clinician- and Patient-Reported CGI-I Scores at Weeks 1, 2, 4, and 8 (FAS, MDE)

	Placebo (N=78)	Droxidopa (N=69)	Difference from Placebo (95% CI)	p-value[1]
Clinician-Reported CGI-I Scores				
Week 1 (Visit 4)				
N	77	69		
Mean (SD)	3.1 (1.02)	2.6 (1.24)	-0.5 (-0.9, -0.1)	0.009
Min, Max	1, 5	1, 6		
Very Much to Slightly Improved, n (%)	45 (58.44)	51 (73.91)		
No Change, n (%)	29 (37.66)	15 (21.74)		
Very Much to Slightly Worse, n (%)	3 (3.90)	3 (4.35)		
Week 2 (Visit 5)				
N	74	68		
Mean (SD)	3.2 (1.14)	2.7 (1.13)	-0.5 (-0.8, -0.1)	0.018
Min, Max	1, 5	1, 5		
Very Much to Slightly Improved, n (%)	40 (54.05)	51 (75.00)		
No Change, n (%)	28 (37.84)	13 (19.12)		
Very Much to Slightly Worse, n (%)	6 (8.11)	4 (5.88)		
Week 4 (Visit 6)				
N	70	65		
Mean (SD)	2.9 (1.09)	2.8 (1.42)	-0.1 (-0.5, 0.4)	0.804
Min, Max	1, 5	0, 6		
Very Much to Slightly Improved, n (%)	45 (64.29)	44 (68.75)		
No Change, n (%)	23 (32.86)	12 (18.75)		
Very Much to Slightly Worse, n (%)	2 (2.86)	8 (12.50)		
Week 8 (Visit 7)				
N	65	58		
Mean (SD)	3.2 (1.19)	2.7 (1.33)	-0.5 (-1.0, -0.1)	0.028
Min, Max	1, 6	1, 6		
Very Much to Slightly Improved, n (%)	31 (47.69)	39 (67.24)		
No Change, n (%)	29 (44.62)	14 (24.14)		
Very Much to Slightly Worse, n (%)	5 (7.69)	5 (8.62)		

	Placebo (N=78)	Droxidopa (N=69)	Difference from Placebo (95% CI)	p-value[1]
Patient-Reported CGI-I Scores				
Week 1 (Visit 4)				
N	77	69		
Mean (SD)	3.2 (0.94)	3.0 (1.02)	-0.2 (-0.5, 0.1)	0.206
Min, Max	1, 5	1, 6		
Very Much to Slightly Improved, n (%)	45 (58.44)	49 (71.01)		
No Change, n (%)	28 (36.36)	15 (21.74)		
Very Much to Slightly Worse, n (%)	4 (5.19)	5 (7.25)		
Week 2 (Visit 5)				
N	74	68		
Mean (SD)	3.3 (1.09)	3.0 (1.18)	-0.3 (-0.6, 0.1)	0.180
Min, Max	0, 6	1, 6		
Very Much to Slightly Improved, n (%)	41 (56.16)	44 (64.71)		
No Change, n (%)	25 (34.25)	19 (27.94)		
Very Much to Slightly Worse, n (%)	7 (9.59)	5 (7.35)		
Week 4 (Visit 6)				
N	72	65		
Mean (SD)	3.2 (1.02)	3.1 (1.33)	-0.1 (-0.5, 0.3)	0.764
Min, Max	1, 5	1, 6		
Very Much to Slightly Improved, n (%)	41 (56.94)	43 (66.15)		
No Change, n (%)	28 (38.89)	12 (18.46)		
Very Much to Slightly Worse, n (%)	3 (4.17)	10 (15.38)		
Week 8 (Visit 7)				
N	66	63		
Mean (SD)	3.2 (1.26)	3.2 (1.33)	-0.0 (-0.5, 0.4)	0.977
Min, Max	1, 6	1, 7		
Very Much to Slightly Improved, n (%)	36 (54.55)	39 (61.90)		
No Change, n (%)	24 (36.36)	15 (23.81)		
Very Much to Slightly Worse, n (%)	6 (9.09)	9 (14.29)		

ANOVA=analysis of variance; CGI-I=Clinical global Impressions-Improvement; CI=confidence interval; FAS=Full Analysis Set; Max=maximum; MDE=missing data excluded; Min=minimum; SD=standard deviation.

1 Treatment differences tested using an ANOVA model with an effect for treatment.